GRAND CHALLENGES IN PHARMACEUTICAL MEDICINE: COMPETENCIES AND ETHICS IN MEDICINES DEVELOPMENT

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GRAND CHALLENGES IN PHARMACEUTICAL MEDICINE: COMPETENCIES AND ETHICS IN MEDICINES DEVELOPMENT

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EDITORIAL
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Editorial: Grand Challenges in Pharmaceutical Medicine: Competencies and Ethics in Medicines Development

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Editorial on the Research Topic

Grand Challenges in Pharmaceutical Medicine: Competencies and Ethics in Medicines Development

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INTRODUCTION

This Research Topic represents a collaboration between the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) and Frontiers in Pharmaceutical Medicine and Outcomes Research aimed to create further awareness of Pharmaceutical Medicine (PM) as a profession and meet the new challenges of medicines development.

WHY?

The advancement in biomedical sciences extended the concept of medical products to including biological agents, gene and cell therapies as well as drug-medical device combinations. The development and application of these new products can be efficiently done only in complex, multidisciplinary teams combining the know-how of pharmaceutical physicians, clinical investigators, basic and applied bio-medical scientists and other non-medically qualified professionals.

HOW?

This Research Topic covers 11 articles focusing on the evolving challenges in medicines development as related to the standards for performing with competence and the application of ethical principles while working in the pharmaceutical industry, academia, research sites and regulatory agencies.

The circumstances related to the COVID-19 pandemic underscores the role of the biopharmaceutical industry as a key link between basic biomedical discovery and the emergence of novel medicines that prolong or improve life. Medicines development can be

defined as an open system involving patients, investigators and associated staff, regulators, sponsors, research sites, etc. as components interconnected through a series of processes aimed to bring effective and safe medicines into the market and maintain them. Because of the above a *systems approach integrating research into healthcare system*s has been proposed to overcome the current barriers to a cost/effective cooperative process and appropriate management of the risks involved (Meadows, 2008; Johnson et al, 2014; Silva et al, 2015).

THE CHALLENGES

However, a host of challenges confront healthcare authorities worldwide. The challenge is particularly great in therapeutic areas where, despite significant medical need and economic impact, the technical challenges and commercial risk of development serve as disincentives to sponsors. Currently the development and approval of new active substances, with its disproportionate focus on oncology and rare diseases is not in alignment with health care needs in most geographic regions. The origins of this misalignment and approaches to overcome this situation are discussed (Milne and Kaitin) with an urgent call to address these disparities using a multi-stakeholder approach and building consensus for change.

Clinical trials constitute the largest single component in medicines development, representing nearly 40% of the R&D expenses of major companies. However, there is broad agreement that the current clinical trial system is inefficient. The biopharmaceutical industry, governments and regulatory agencies, academic researchers, the medical community and the media should work collaboratively to fill the gaps and create efficient clinical trial networks and trial designs.

The lack of an adequately sized and appropriately trained multi-professional workforce both in the industry-related and the academic clinical research field is also a significant part of the situation. The root of the problem resides in the lack of proper education in clinical research and pharmaceutical medicine at the undergraduate and postgraduate levels across academic institutions worldwide. Only a few universities are directly involved in this process and thus professionals joining the industry usually gain competence through on-the-job training. The outcomes of an IFAPP sponsored international survey aimed to assess the self-perception of competence, education and training needs among biomedical professionals serving in the various functions in the pharmaceutical industry are described (Imamura et al.) indicating low and variable levels of perceived competence for the various domains regardless of the seniority in the job. Similar results were reported among individuals involved in clinical research (Sonstein et al., 2016) underscoring the need for proper education and training (E&T) worldwide.

The evolution of postgraduate vocational E&T in pharmaceutical medicine along with the development of the full set of core competencies (knowledge, skills, behaviors and attitudes to perform a task) for pharmaceutical physicians and drug development scientists within the competence framework of seven domains are now established (Stonier et al.). Core Competencies in Clinical Research have also been identified and proposed as a model for E&T and improving the quality and accountability for specific functions involved in the drug development process (Sonstein and Jones) including the challenges for implementation and lessons learned.

Many of the disruptive forces affecting the healthcare industry today are also impacting education. The increasing voice of the patient and the rise of patient engagement in drug development are mirrored by the increasing student voice and student focus on education. The process for curriculum transformation from didactic to competency based programs in Pharmaceutical Medicine in Australia is thoroughly described (Chisholm) whereas the process of adoption of the scope of the above Framework to reflect such roles in academic institutions or regulatory bodies in Switzerland is part of the lessons learned (Schnetzler et al.).

USE OF COMPETENCY BASED EDUCATION

There is a growing consensus of the role of vocational training to gain competence (UNESCO, 2019). Specific vocational programs in medicines development have been implemented in the UK and Ireland for several years leading to a national medical board certification in Pharmaceutical Medicine. IFAPP and PharmaTrain developed the vocational Specialist in Medicines Development Program sponsored by the IMI. The outcomes of pilot experiences in Italy and Japan are encouraging (Criscuolo et al.) with recommendations to all other countries and institutions which may consider establishing this program.

Regulatory Affairs professionals play pivotal roles to ensuring healthcare products adhere to regulations and in gaining regulatory approvals for product manufacture and sales. Although they perform complicated work connected to the entire product lifecycle, only 14% of regulatory professionals come to the field with a degree related to the work (Regulatory Affairs Professional Society, 2018) and more than half are involved in regulatory work as a second career. Professional Associations are key in making efforts to develop and align competencies for regulatory professionals and create a competent global regulatory workforce (Bridges).

ETHICAL CONSIDERATIONS

The complexity of developing and applying increasingly sophisticated new medicinal products has led to the participation of many medical and non-medically qualified scientists in multidisciplinary non-clinical and clinical drug development teams worldwide. Revising the IFAPP International Code of Ethical Conduct for Pharmaceutical Physicians written in 2003, the Ethics Working Group prepared the IFAPP International Ethics Framework (Kerpel-Fronius et al.) with the intention to provide recommendations to both professional groups to make joint ethical decisions during

various situations occurring during clinical trials. Mutual trust and respect between the various experts is emphasized as the basis of effective multi-professional team work.

These revised recommendations add to the list of Codes of Practice for pharmaceutical physicians prepared by professional organizations like the Faculty of Pharmaceutical Medicine, CIOMS and the World Medical Association. Jointly they provide clear and detailed guidance for correct behavior of pharmaceutical medicine experts in specific research situations (Morris et al.).

An alignment of the Declarations of Helsinki with that of the Declaration of Taipei is recommended for the better protection of both biological materials and data derived from clinical studies when their secondary use is intended. Furthermore, it is emphasized that any future plan for data and/or material sharing should be explained in the protocol, signed by the research participants and should be made publicly available (Kurihara et al.).

This Research Topic intended to create further awareness of the complex set of competencies and ethical considerations required for clinical drug development and the need to foster education and training at the undergraduate, postgraduate and continuing professional development levels to ensure the pharmaceutical industry is fledged with competent professionals able to bring better and valuable medicines to the market place and contribute to leveraged health in their communities.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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PERSPECTIVE
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The Shared Ethical Responsibility of Medically and Non-medically Qualified Experts in Human Drug Development Teams

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The complexity of developing and applying increasingly sophisticated new medicinal products has led to the participation of many non-medically qualified scientists in multi-disciplinary non-clinical and clinical drug development teams world-wide. In this introductory paper to the "IFAPP International Ethics Framework for Pharmaceutical Physicians and Medicines Development Scientists" it is argued that all members of such multidisciplinary teams must share the scientific and ethical responsibilities since they all influence directly or indirectly both the outcome of the various phases of the medicines development projects and the safety of the research subjects involved. The participating medical practitioner retains the overriding responsibility and the final decision to stop a trial if the well-being of the research subjects is seriously endangered. All the team members should follow the main ethical principles governing human research, the respect for autonomy, justice, beneficence and non-maleficence. Nevertheless, the weighing of these principles might be different under various conditions according to the specialty of the members.

Keywords: ethics, ethics committee, medicines development, pharmaceutical medicine, multidisciplinary research

For hundreds of years, treatments based on experience formed a continuum with uncontrolled individual therapeutic trials performed by the treating physicians in the hope of helping their patients. The deep ethical concern of the practicing physicians is expressed with great clarity by William Withering who introduced digitalis into medical practice in the 18th century: "After all, in spite of opinion, prejudice or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind." (Eichhorn and Gheorghiade, 2002).

The major shift toward prospective clinical trials can be traced back to the end of the nineteenth century when major hospitals were founded where trained medical personnel could perform well planned clinical trials. In addition, the creation of medical journals meant that the results could be rapidly communicated to other medical teams working world-wide, creating an international background for establishing common norms for accepted medical practice. Unfortunately, in the rapidly changing medical research environment some physicians performed human experiments which clearly violated the broadly accepted ethical principles of society. During this period the German scientific community, represented by outstanding clinical scientists such as Rudolf Virchow, Robert Koch, Paul Ehrlich, and Emil von Behring made breakthrough contributions to medicine.

It is therefore not surprising that the first regulation of clinical experiments was penned in Germany in 1901 (Erlass der Preussischen Regierung vom Dezember, 1901) in which most of the major ethical issues of clinical research at the time were listed. The complexity of contemporary medical interventions could be relatively easily managed by the clinicians without extensive support of other non-medically qualified experts. Accordingly, it was a reasonable decision by the law makers to place the entire ethical responsibility on the head of the medical team and proclaim that it was the duty of the senior chief physician to evaluate both the scientific and ethical aspects of the research plan and supervise its execution according to Hippocratic Oath governed primarily by the maxim "primum non-nocere."

In practical terms the responsibility for the safety and well-being of the trial subject means that the ethical responsibility is essentially also the burden of the medical profession. It is explicitly stated in the Declaration of Helsinki: "It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects." (WMA Declaration of Helsinki, 2013).

It has been tacitly assumed that the ethical guidance will be followed by the other non-medically qualified personnel. This strong relation of human research to the human health field and profession has been followed essentially unchallenged in the other ethical declarations, guidelines and international agreements dealing with human research published subsequent to the Nuremberg trial (The Belmont Report, 1979; The Oviedo Convention, 1997; Good Pharmaceutical Medical Practice, 2014; ICH Harmonised Guideline, 2016; International Ethical Guidelines for Health-related Research Involving Humans Final CIOMS, 2016). The ICH Harmonized Guideline refers only shortly to multidisciplinary research stating that "the investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties." In the CIOMS Guideline prepared in collaboration with the World Health Organization (WHO) it is only recommended that sponsors, researchers and research ethics committees "must ensure that all research personnel are qualified by virtue of their education and experience to perform competently and with integrity. This includes receiving appropriate ethics education and training. Qualifications of research personnel must be adequately described in the materials submitted to the research ethics committee." Rapid scientific progress makes it, however, questionable whether this narrow approach is tenable, or the ethical issues should also be specifically addressed with inputs from other experts specifying also their ethical responsibilities.

Medical treatments became very sophisticated in recent years, many complex interventions can be performed only with the support of highly trained but non-medically qualified personnel. This is of great concern primarily for drug development groups which investigate for example advanced medicinal products such as gene and cell therapies, drug and medical device combinations. In such multidisciplinary teams the physicians work as team members, with special ethical responsibility to care for the well-being of the patients. Therefore, the physicians maintain a well-defined safeguarding role within the team, although he/she may no longer be in the position to understand the inputs of the various professionals in depth. Consequently, the physician of such teams cannot carry the entire ethical responsibility for the correct planning and conduct of the clinical trial alone. Inevitably the society has to decide whether the traditional clinician-centered ethical guidelines should be maintained or whether it is time to address the ethical responsibilities of the various non-medically qualified professionals directly involved as well.

The clinicians and non-medically qualified scientists have two main fields of interactions in the clinical development and application of medicines. The first occurs in translational medicine. The second contact is characterized by strong multidisciplinary cooperation in the development and therapeutic application of advanced therapies. As a result of the increasingly critical interaction of basic scientists with medical professionals many non-medically qualified scientists have become members of the IFAPP (2003). At present a large fraction of the IFAPP membership is not medically qualified, although pharmaceutical medicine was originally conceived as a medical discipline. It is a logical further step, that IFAPP decided to consider the ethical aspects of this collaboration and started to characterize the ethical responsibilities of the many non-clinicians involved in the research and clinical application of modern complex therapies. **Supplementary Material**: IFAPP International Ethics Framework for Pharmaceutical Physicians and Medicines Development Scientists, 2018.

Translational medicine provides a scientific bridge connecting non-clinical studies with the early exploratory evaluation of an investigational medicinal agent in humans (Littman et al., 2007). In reality, drug development gradually became part of an enlarged concept of pharmaceutical medicine. The safe and effective transfer of basic research results into the human research phase became a primary concern. New drug targets and biomarkers, the development of drug-medical device combinations, the methods of the preparation and administration of gene or cellular medicinal products are usually first investigated in animals by academic research groups. It is therefore very disappointing that from 53 landmark studies published in prestigious journals only 6% reported sufficiently robust data to drive reliably human medicines development programs (Begley and Ellis, 2012). Similarly, from 67 projects evaluated by a company 65% of the results published in the scientific literature could not be reproduced (Prinz et al., 2011). The broad experience of industrial R&D experts indicates that

around 50% of findings published cannot be reproduced by the pharmaceutical industry (Booth, 2011). The inability of industry and clinical trial groups to reproduce the results of many academic publications on potential therapeutic targets and biomarkers suggests a general systemic problem, although occasional fraud cannot be ruled out.

Promising pre-clinical testing results frequently lead to rapid clinical development without thoroughly evaluating the quality of the data and the reproducibility of the experiments. This practice might lead, in unfortunate cases, to serious human suffering and wasting of valuable clinical resources. Superficially performed and/or interpreted animal-human translation studies might be considered one of the main components leading to system failures occurring in human phase I studies. Examples of two recent early clinical trial tragedies caused by TGN-1412 (TeGenero Immuno Therapeutics AG), (Reason, 2000; Suntharalingam et al., 2006; Sims, 2009; Attarwala, 2010), and by BIA 10-2474 (Bial-Portela & Ca. SA.) (Kerbrat et al., 2016; Greenberg et al., 2017) reminded the scientific community of the consequences for involved human beings. It became a main ethical requirement for effective and safe human drug development, that academic scientists should adopt research methods similar to those used in clinical trials to significantly improve construct validity of their research, especially the internal and external validities of the confirmatory pharmacotherapeutic studies in animals (Kilkenny et al., 2010; van der Worp et al., 2010; Arrowsmith, 2011; Kimmelman and London, 2011; de Vries et al., 2014; Kimmelman et al., 2014). With the translational concept animal and human studies gradually grow together to form a functional continuum. This bridge effectively binds experts of non-clinical research and clinical drug development into a functional continuum of partnership with shared ethical responsibilities. As a logical consequence it was considered necessary to include the ethical responsibilities of non-clinical researchers into the new revised version of the ethical framework of IFAPP.

Multidisciplinary teams gained broad acceptance in drug development when, beside the determination of clinical efficacy and safety, the correlations between the plasma level of the drugs and their pharmacodynamic effects also became the additional focus of clinical pharmacological investigations. Such cooperation is primarily characterized by the parallel work of the clinical and various non-medical experts who perform pharmacokinetic, biochemical, immunological and other investigations on human samples. The ethical problems of such cooperation are usually limited to the amount and frequency of the sampling of human materials needed for conducting the studies. The situations can be handled by finding a scientifically acceptable compromise which does not cause additional harm for the human subjects. A conceptually entirely different and much more sophisticated cooperation becomes necessary for investigating and applying advanced therapeutic products in patients.

The complexity of the scientific-medical approach can be convincingly demonstrated in the case of the recently developed Chimeric Antigen Receptor Adoptive T-cell (CAR-T) cancer therapy. For this treatment the genes coding for the specific CAR-T receptor recognizing the cancer surface antigen(s) of the individual patients must be transferred into the harvested T-cells of the patients. The modified T-cells are then further incubated *in vitro* before re-transfusion for reaching the required number of modified T-cells for effective tumor kill. The production of the individually prepared targeted medicinal product is carried out under Good Manufacturing Practice (GMP) conditions by a multidisciplinary expert team specialized in immunology, cell and molecular biology (Jacobson and Ritz, 2011; Yee, 2013; Sharpe and Mount, 2015; Hartmann et al., 2017). The therapy is a real team effort. The final therapeutic decisions must be made jointly by all the experts involved considering both the condition of the patient as well as the success and specificity of the CAR-T cell preparation to be used for the individualized therapy.

In such multidisciplinary teams the physician is only one member with a specific right to stop the intervention if the safety of the patient is endangered and the interruption of the therapy does not cause additional harm. It is not surprising that the FDA requires that the entire staff involved in this complex therapy should be specifically trained and certified (FDA News Release, 2017). The joint scientific-ethical responsibility of such a multidisciplinary team is obvious. Although it is assumed that all experts act according to the basic principles governing human research, respect for autonomy, beneficence, non-maleficence and justice (Beauchamp and Childress, 2012), different weighing of these principles might be expected under different conditions (Ebbesen and Pedersen, 2007; Page, 2012). Such differences must be resolved within the group for each case separately. To maintain successful cooperation, it must be ensured that each contributor is able to work according to the guiding principles of their professional organizations.

The rapid progress of advanced therapies will further increase the need for including many different professionals into clinical teams. In addition, new scientific knowledge continuously generates unforeseen ethical problems. For successfully managing increasingly sophisticated ethical challenges IFAPP recommends and plans to contribute to the strengthening education of ethics at the under-graduate and post-graduate levels both for medical and other biomedical professionals.

The aim of the linked IFAPP International Ethics Framework is to highlight the ethical issues relevant to the increasingly close cooperation of physicians and non-medically qualified experts in human drug development and application. **Supplementary Material**: IFAPP International Ethics Framework for Pharmaceutical Physicians and Medicines Development Scientists, 2018. The intention of the IFAPP Working Group on Ethics was to provide recommendations for supporting both medically and non-medically qualified investigators to make ethical decisions cooperatively under various, frequently unexpected, situations occurring during human drug research. We are convinced that the recommended joint decision-making process will be helpful for all scientists working all over the world in medicines development to find ethical answers to new challenges. It is also hoped that the revised edition of the IFAPP International Ethics Framework might be helpful for countries either to adjust their local

recommendations to the new scientific environment or to introduce ethical guidance if not yet existent in their country.

AUTHOR CONTRIBUTIONS

All authors contributed both to the development of the ideas as well as to the writing of the paper and the linked **Supplementary Material**: IFAPP International Ethics Framework for Pharmaceutical Physicians and Medicines Development Scientists (PPs & MDSs).

SUPPLEMENTARY MATERIAL

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REVIEW
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Joint Task Force for Clinical Trial Competency and Clinical Research Professional Workforce Development

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Clinical research workforce development efforts have focused on both increasing the size of the workforce of investigators and professionals working in the clinical research enterprise, but also the education and training of those individuals to ensure the quality of study performance to improve the public's health. A major contribution to these efforts has been the establishment of core competencies for clinical research professionals by the Joint Task Force for Clinical Trial Competency. This article reviews the development of the clinical research core competencies, their wide adoption and influence on job descriptions, education, training, and academic accreditation.

Keywords: competence, competency, workforce development, clinical research, portfolio, professional development, accreditation

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INTRODUCTION

It is widely agreed upon that there has been a significant increase in both the number and the complexity of clinical trials during the past decade. The number of registered clinical trials as of June 22, 2018 is 276,190 up from 231,208 just a year ago[1]. The global clinical trial service market is predicted to reach $64B by 2020 (Centerwatch, 2017). The demand for clinical research professionals (CRPs) already exceeds the supply and the pressure to grow the clinical research workforce will undoubtedly continue. The underlying solution is much more complex than just recruiting, educating and training new students to become CRPs and increase the size of the workforce.

DEVELOPING THE CLINICAL RESEARCH WORKFORCE

There is no required educational background or defined set of competencies that are necessary to become a CRP. The majority of the current workforce has been trained "on the job." Very few enter the clinical research profession as a direct result of undergraduate education or knowledge of the field. An understanding of the professional roles in clinical research, adequate onboarding, an understanding of the ethical underpinnings of the profession and an ability to grow professionally

Abbreviations: ACRPs, Association of Clinical Research Professionals; CAAHEPs, Commission on Accreditation of Allied Health Education Programs; CoAPCR, Consortium of Academic Programs in Clinical Research; CRP, clinical research professional; ICH, International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IDP, individual development plan; JTF, Joint Task Force for Clinical Trial Competency; KSAs, knowledge, skills and attitudes; MRCT, Multi-Regional Clinical Trial Center; NIHR, National Institute for Health Research; SoCRA, Society of Clinical Research Associates; SOP, standard operating procedure.

[1] ClinicalTrials.gov

and move upward in an organization are key elements that are required to be successful in the field. Onboarding training in clinical research is typically minimal or poorly organized (Sonstein et al., 2014). Though most individuals, with time, become skilled at their current roles, as the responsibilities of their role changes with increasing technological and quality demands, or new opportunities arise, individuals find themselves moving from proficient to novice repeatedly. In this era of increasing role complexity, the lack of professional requirements and potential educational gaps can lead to role dissatisfaction and personnel turn-over, a costly by-product.

During the past decade academic programs have been developed to educate and train physician investigators, clinical research coordinators, clinical trial monitors, regulatory affairs professionals, and clinical data managers. The graduates from these programs are highly qualified and anxious to enter the market, but unfortunately, the hiring criteria almost always require varying levels of previous experience. It is assumed that experience equates with competence. For most other health-related professions, professional certification or licensure is recognized as competence. Entry level individuals are required to have a specific academic degree, often an internship or other hands-on experience and have passed an examination which is administered under the aegis of a representative professional or licensure organization.

There are two widely recognized professional organizations which offer professional certification to CRPs. The ACRPs and Society for Clinical Research Associates (SoCRA) both require a minimum of 2 years' documented clinical research work experience to be eligible for their qualifying examinations (Association of Clinical Research Professionals, 2018b; Society of Clinical Research Associates, 2018). The 2-year standard, based solely on time of employment rather than competence, contributes to the current shortage of clinical research workforce personnel. Individuals who have completed academic programs in clinical research are still required to document previous experience in order to qualify to sit for certification examinations, but the requirement may be lessened to 1 year for approved programs. Nevertheless, this experience criterion has created a "Catch-22" situation where you need experience to get a job and professional certification, but you need a job to get experience and professional certification.

Not only does the clinical research workforce solution require an influx of new qualified professionals, but it requires that the current workforce continuously enhance their competency through professional development activities. Clinical research quality assurance and training requirements are mandated in the updated International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines (International Council for Hamronisation of Technical Requirements for Pharmaceuticals in Human Use, 2016) and the Declaration of Helsinki (World Medical Association, 2013), but again, there has been until recently, no generally agreed upon set of core competencies upon which educational programs and training requirements for either entry level professionals or continuing professional development would be based.

THE JOINT TASK FORCE FOR CLINICAL TRIAL COMPETENCY- SETTING THE PROFESSIONAL STANDARD

Professionalization is defined as the process by which "any trade or occupation transforms itself through the development of formal qualification based upon education, apprenticeship, and examinations, the emergence of regulatory bodies with powers to admit and discipline members, and some degree of monopoly rights" (Bullock and Trombley, 1999). Roles associated with CRPs have evolved through a process of delegation from principal investigators (Mueller, 2001). Over time, those roles have evolved and resulted in a workforce of highly skilled professionals that are integrated across the clinical research enterprise. To become recognized as a profession, certain characteristics should be in place. Hinkley et al. (2015) highlight these characteristics as a "mature" profession being: (1) accredited professional education; (2) skills development (core competencies); (3), Licensing; (4) Professional Development; and (5) Code of Ethics. Licensing of all members of the clinical research profession is a controversial issue, but may be a necessary characteristic depending on role and scope of practice (e.g., clinical research nurse; physician principal investigator, pharmacist, etc.). Overall, the still evolving profession of clinical research is meeting these characteristics and continues to make significant strides toward maturing the profession and in workforce development.

During the spring of 2013, at a meeting of representatives from pharmaceutical companies, contract research organizations, academic institutions, clinical research sites and professional societies, hosted by the MRCT at Harvard University, the JTF was formed. During the following year, the JTF members collaborated to develop a single, high-level set of standards that could be adopted globally and serve as a framework for defining professional competence throughout the clinical research enterprise. The JTF Framework is composed of 8 Domains (**Figure 1**) and 48 core competency statements which were aligned and harmonized utilizing published statements of core competency requirements which cover the entire clinical research enterprise.

The standards developed by the JTF incorporated formal input from a variety of United States and international stakeholders from academic institutions, non-profit organizations and the private sector (Sonstein et al., 2014). The JTF Core Competency Framework has been widely recognized globally as the standard for skills development and competency (Kremidas, 2017). Many federally-sponsored research initiatives in the United States have adopted the JTF Framework to help define workforce development at Clinical and Translational Science Award funded institutions (Calvin-Naylor et al., 2017). Materials and adoptions of the JTF Framework have been widely disseminated at conferences, in the manuscripts cited herein, and on the JTF Website (Joint Task Force for Clinical Trial Competency, 2017b). The JTF is currently receiving administrative and website support from the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University. One of the highly significant adopters of the JTF Framework has been by ACRP. This global organization represents more than 13,000 CRPs

FIGURE 1 | Joint Task Force for Clinical Trial Competency Core Competency Domains.

and has restructured their annual meeting into sessions which follow the JTF Framework Domains. As concerns professional certification, ACRP has realigned their personnel certification examinations based upon the same Domains. Following suit, the SoCRA also re-aligned their certification exam to the JTF Framework. While licensing is not required for all roles in the clinical research profession, it is applicable for specific clinical roles. Moreover, certification has become a standard in the profession.

The JTF acknowledged that the dynamic nature of the clinical research enterprise would necessitate that the JTF Framework would require ongoing updating as technological and regulatory changes occurred to the clinical trial process. Recently, the JTF Framework was updated to clarify terminology, to refine the organization and description of certain competencies, and to be inclusive of clinical research beyond clinical trials alone (Joint Task Force for Clinical Trial Competency, 2017a). This can be viewed online at the JTF Website. Ongoing review by the JTF will determine future updates of the Framework.

Traditionally, the academic recognition of a profession is made by peers and by organized practitioners through an accrediting body. In 2012, the profession of clinical research was recognized by the CAAHEPs, opening the door to the establishment of curriculum standards and a pathway to clinical research education program accreditation by CAAHEP (Commission on Accreditation of Allied Health Programs, 2012). There are currently 100s of academic programs which educate CRPs in United States, Canada, Europe, Africa, Asia, India, and Australia. Many of these programs are members of the COAPCR and have mapped their curricula to the JTF Core Competencies in preparation for future accreditation applications. Checklists to aid in training or academic course mapping can be found on the JTF website http://clinicaltrialcompetency.org.

Further compromising clinical research workforce development has been inconsistency in job titles and professional progression. A recent survey of CRPs indicates that the most common reason for turnover among CRPs is lack of professional progression, training opportunities, and professional development (Applied Clinical Trials, 2018). The JTF Framework has been used to address job predictability and professional advancement. Duke University utilized the JTF Framework to restructure job titles and progression pathways which reduced the number of job titles from 80 to 12 and led to greater consistency and predictability (Brouwer et al., 2017b). Professional descriptions further defined levels of clinical research experience as Fundamental, Skilled and Advanced in order to create professional ladders. Others have also utilized the JTF Framework to define specific role responsibilities (Association of Clinical Research Professionals, 2017, 2018a). In 2016, the American Nurses Association recognized the specialty of Clinical Research Nursing (American Nurses Association and International Association of Clinical Research Nurses, 2016).

Members of the JTF have participated in numerous international collaborations which are highlighted on the JTF Website[2]. For instance, PRAXIS Australia, Ltd. created Research Essentials comprised of 68 accessible modules and electives which is based on the JTF Framework and the United Kingdom NIHR Clinical Research Network has used a competency-based approach to create the Integrated Workforce Framework (Joint Task Force, 2018). International training efforts are being developed by JTF members to include competency-based modules for workforce development in India and in South America (personal communication, Jones, 2018) and via PharmaTrain.

Ongoing debate related to education, experience, and hiring practices prompted a global survey of CRPs that addressed self-perceived competence and the relevance of the JTF Framework to their roles (Sonstein et al., 2016). Responses to the survey were received from CRPs in the United States, Europe, Latin America, Asia, and Australia and represented all of the major professional roles. Analysis of the results of the survey showed that the domains and core competency statements within the JTF Framework were relevant globally, but also indicated that specific roles differed between regions in their competency requirements. Additionally, it became clear that there was a need to acknowledge the increase in level of competence that occurs as individuals move forward in their careers. As one gains experience and moves into a leadership or mentoring role, the level of competence should increase. In addition, certain roles within the enterprise require differing levels of competence in different domains. For example, a study site supervisor in a data management role would need high level competencies in the Data Management and Informatics and the Leadership and Professionalism Domains, but would not require such competencies in the Scientific Concepts and Research Design or Investigational Products Development and Regulation domains. As noted above, it has been shown that in different areas of the world and under different regulatory authorities, the competency requirements for certain roles differ. For many South American countries, for example, the role of Clinical Research Coordinator is uncommon: Principal Investigators (PIs) are directly responsible for clinical trial implementation (Silva et al., 2017). Thus, PIs in this region of the world would need higher level competencies in the Clinical Trial Operations and Site Management Domains.

APPLYING A LEVELED APPROACH FOR TARGETED WORKFORCE DEVELOPMENT

Clinical research stakeholders suggested that broader adoption and utility of the JTF Framework would be facilitated by defining the competencies at Fundamental, Skilled and Advanced levels so that they could be applied across a wider range of roles. A recent manuscript reviews the process undertaken by the JTF to generate leveled competencies for CRPs across the broad spectrum of roles that characterize the enterprise and the product of that effort (Sonstein et al., in press). Examples of measurable competency assessments at each level are provided as a supplement to this manuscript and are designed to facilitate their application in workforce development initiatives across the clinical research enterprise.

Several groups have targeted a similar approach for clinical research competencies or skillsets for particular roles in clinical research. The ACRP has used a stakeholder approach to develop leveled competencies for study coordinators and clinical research monitors, two groups that ACRP has targeted for certification (Association of Clinical Research Professionals, 2017, 2018a). The Oncology Nursing Society published the 2016 Oncology Clinical Trials Nurse Competencies, updating their previous versions to include a leveling approach (Oncology Nursing Society, 2016). The United Kingdom NIHR produced an Integrated Workforce Framework as a resource for CRPs and nurses working in the NIHR Clinical Research Network that is intended to be used as a self-assessment tool for four levels of CRPs (National Institute for Health Research, 2017). The Regulatory Affairs Professional Society has produced a leveled approach for their Regulatory Affairs Core Competencies (Regulatory Affairs Professional Society, 2016). The Global Health Network has launched a competency framework for low and middle income global clinical researchers working in tropical diseases (Training in Tropical Diseases and The Global Health Network, 2016). Duke University applied the JTF Framework to employ a "tiered" approach to professional progression across several job families, such as study coordinators, clinical research nurses, regulatory coordinators, and research program managers (Brouwer et al., 2017a,b).

Intentionally, the JTF leveling work was not directed to any specific role within the clinical research enterprise. In addition, the international relevance of the effort was ensured by including non-United States representatives in each of the five workgroups which contributed to the work. The JTF Leveled Competency Framework (see **Supplementary Table 1**) is intended to provide direction for those who are creating training programs, specialized role descriptions, or professional progression planning for clinical research positions and may be adjusted to site-specific practice cultures. This framework helps to define the central skills and competencies that professionals at various levels of proficiency require in order to plan, conduct, or manage clinical research. Moreover, this leveled competency framework is intended to be internationally applicable.

One of the more difficult aspects of workforce development is the actual assessment of an individual's competence. The JTF used Bloom's Modified Taxonomy (Anderson and Krathwohl, 2001) and developed specific examples for each competency level which provided an intentional approach that described KSAs, ranging from "novice to expert" (Benner, 1984), as an initial step to use for competency assessment and consistent expectations in an organization, particularly when it is difficult to align across departments, divisions, research groups, or global regions.

The clinical research enterprise employs individuals in a variety of roles and at varying levels of expertise. Given the global expansion and increasing complexity of the enterprise, and the documented shortage of qualified clinical research personnel,

[2]www.clinicaltrialcompetency.org

addressing the workforce development needs has become a priority worldwide (Li et al., 2015; Miseta, 2016; Howes, 2017; The Economist Intelligence Unit, 2018). The JTF Framework Fundamental level provides a series of standards to describe the role and training needs of new entry level professionals. The Skilled level competencies define the professional expectations for experienced, mid-career CRPs and can serve as a model for upward mobility and career development. The Advanced level competencies provide guidelines for managers, mentors and other leadership roles within the enterprise as well as aspirational goals for those hoping to move into leadership roles.

The Leveled JTF Framework complements previous work and offers a generic entry level goal for the education and training of new CRPs; a definition of demonstrated competencies that human resource professionals, managers, and educators can use for assessments and career mobility; and goals for leadership and mentoring roles within the clinical research enterprise. The provision of the additional granularity of "levels" to the individual competencies, and the assessment criteria, renders transparent a pathway for professional development and organizational consistency. Using a leveled approach to writing job descriptions or progression planning, individuals have a more objective method of professional role progression which leads to better staff opportunity and job satisfaction.

CONTINUING PROFESSIONAL DEVELOPMENT AND COMPETENCY ASSESSMENT

As more groups adopt the JTF Framework, new approaches for assessment of competence, the application of individual professional development planning (IDP) and ePortfolios may stimulate workforce development and demonstrated competence. Portfolios are collections of educational and work-related documents that showcase the progression of acquired KSAs as a learner or professional. Early use of portfolios was paper-based, where documents were collected and filed in a notebook. Electronic formats for portfolios, called ePortfolios are now being used. Not only are portfolios used to showcase work, they can also be used to document continuing education and professional activities and as a forum for documenting development goals. EPortfolios are used as an assessment tool for professional role development. Moreover, the use of ILPs or "individualized learning plans" have been used in medical education whereby medical residents engage in competency-based self-directed learning by setting short-term SMART (specific, measurable, accountable, realistic, timely) goals and a mentored approach for demonstrating goal and learning acquisition (Hernandez et al., 2017; Kastenmeier et al., 2018). Similarly, IDPs have been used in mentored clinical and translational investigator training to expand the numbers of clinician-scientists (Fuhrmann et al., 2018). The JTF Framework has been used as a competency-based approach to stimulate individual professional and learning development and to demonstrate KSAs through ePortfolios, in formal education and workforce development areas (Association of Clinical Research Professionals, 2016; Jones et al., 2016; The Ohio State University, 2018). Such applications of ePortfolio are being implemented in CRP development across federally-funded research sites in the United States; as a potential system to improve the assessment of applicants to contract research organization jobs (personal communication, W. Gluck); and, to assist in measuring acquired KSAs for job promotions (Shiner, 2009).

Elements of an ePortfolio system would include showcasing KSAs that illustrate competence by JTF Core Competency Domain (**Figure 1**). For example, a study coordinator may upload an SOP, a recruitment plan, a participant educational flier, and an innovative informed consent checklist to an ePortfolio to show "experience" in the Ethical and Participant Safety and Clinical Trials Operations domains. The ePortfolio model provides a competency-based approach for showcasing experience and can be used for internal organizational evaluation and upward mobility as well as by an individual seeking employment to demonstrate competence and supplement existing social media sites such as LinkedIn. Today's employers are more influenced by an ePortfolio over a paper-based resume (Leahy and Filiatrault, 2017).

CONCLUSION

In Summary, the JTF Framework has become a global resource. Though regulatory guidelines and implementation mechanisms differ from region to region, the JTF Framework provides a universal standard and a valuable foundation for initiatives that are seeking to increase the size, competency, and professionalization of the workforce responsible for the design, conduct, and oversight of clinical research.

AUTHOR CONTRIBUTIONS

SS and CJ contributed equally to the writing and editing of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2018.01148/full#supplementary-material

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Evolution to a Competency-Based Training Curriculum for Pharmaceutical Medicine Physicians in Switzerland

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In Switzerland, Pharmaceutical Medicine has existed as one of 46 physician specialties accredited by the Federal Office of Public Health for more than 20 years. As a medical-scientific discipline, our goal is to enable best possible therapeutic coverage for the benefit of patients and society through a medical need-based development and optimal use of medicinal products. The role of the specialist in Pharmaceutical Medicine is to closely collaborate with various stakeholders of the healthcare system in the context of the discovery, research, development and approval of new medicinal products, as well as safe and effective use of new and established medicinal products in daily clinical practice. The post-graduate training consists of 2 years of patient-related clinical work, followed by 3 years of vocational training at certified training centers in Pharmaceutical Medicine. This also includes completion of an academic post-graduate diploma in Pharmaceutical Medicine (30 ECTS) according to the IFAPP/PharmaTrain syllabus and a 1 day board exam. As part of an ongoing revision of the training curriculum, we are developing a Swiss Catalog of Core Competencies in Pharmaceutical Medicine (SC^3-PM), based on the IFAPP competency framework for drug development specialists in industry. In this article we discuss how we adapt the scope of the IFAPP competency framework to better reflect such roles in academic institutions or regulatory bodies in Switzerland.

Keywords: Pharmaceutical Medicine, competency-based, post-graduate training, board-certification, vocational training, Switzerland

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PHARMACEUTICAL MEDICINE TRAINING IN SWITZERLAND

On January 1, 1999, the Swiss Department of Health officially recognized Pharmaceutical Medicine as a fully board-certified physician specialty in Switzerland. This marked a key milestone for the Swiss Society of Pharmaceutical Medicine (SSPM). The SSPM was founded mid 1997 with the aim of advancing the science and practice of Pharmaceutical Medicine, by developing and maintaining competencies, ethics and integrity in order to provide the highest professional standards for the benefit of the patients and public (Traber and Althaus, 2010). Today, Pharmaceutical Medicine is one of 46 physician specialties accredited by the Swiss Department of Health

(Swiss Institute for Post-Graduate Training and Continuous Education, 2018c), and Switzerland is still one of the few countries where such a board-certified physician specialty exists (Nell, 2018).

A board-certified specialist title is the reference for the post-graduate qualification of a physician in Switzerland and is publicly disclosed in the national registry of medical professionals (Federal Office of Public Health, 2018b). For most specialties it is the pre-requisite to practicing independently and being remunerated for related clinical activities. There are no clinical or regulatory activities restricted to a physician who is specialized in Pharmaceutical Medicine, however, the title serves as evidence of the qualifications required by the Swiss Clinical Trials Ordinance to act as sponsor-investigator (Swiss Clinical Trials Ordinance, 2017).

Since its introduction, the training curriculum for Pharmaceutical Medicine requires 2 years of patient care related clinical training, followed by 3 years of vocational training at certified training centers for Pharmaceutical Medicine (reviewed in Traber and Althaus, 2010). This general educational framework for postgraduate training for physicians in Switzerland is governed by the Swiss Institute for Post-Graduate Training and Continuous Medical Education (Schweizerisches Institut für Weiter- und Fortbildung, SIWF), while the SSPM is responsible for the subject specific content of the curriculum (see **Supplementary Figure S1**) (Swiss Institute for Post-Graduate Training and Continuous Education, 2018b). Training centers are classified in four categories (A–D) based on multiple parameters such as the number of board-certified (or comparably qualified) educational staff as well as metrics and infrastructure regarding various domains offered for training from the broad spectrum of Pharmaceutical Medicine.

Historically, clinical trials were defined as the core element of medical product development, which has been reflected in the educational goals and requirements. Trainees had to demonstrate at least 2 years of project level involvement in clinical trials and training centers were classified based on number of CRFs actively managed in phase I–IV trials, as well as metrics on adverse event reports. Training center activity in the area of drug discovery, pre-clinical development, pharmacological development and public health had a lower weight. The main focus on clinical trials has gradually been removed and since the last revision in 2016 all core areas are contributing now in a balanced way to the vocational training for Pharmaceutical Medicine (Swiss Institute for Post-Graduate Training and Continuous Education, 2018d) (see **Supplementary Table S2**).

Each training site has to prepare its own concept for vocational training based on the educational goals outlined in the current training curriculum for Pharmaceutical Medicine (Swiss Institute for Post-Graduate Training and Continuous Education, 2018d). This serves as the basis for validation through a SIWF-led expert panel (including one SSPM representative), which grants approval of new training sites, renewal in case of change of training center lead at an approved site, or general periodic audits (at least every 7 years). Additionally, each trainee is required to attend and document a minimum of 360 h of theoretical training on the topics of discovery (12 h), pharmaceutical development (16 h), pre-clinical development (24 h), clinical development (150 h), pharmacovigilance (32 h), medical information (32 h), drug regulations (46 h), socioeconomics and public health (24 h) as well as management (24 h). This can be substituted by successful completion of an academic post-graduate diploma course following the IMI/PharmaTrain syllabus (PharmaTrain, 2018), which is offered in Switzerland by the European Center for Pharmaceutical Medicine (ECPM) (European Center for Pharmaceutical Medicine, 2018) at the University of Basel. Learning progress is evaluated by the training center leads using regular structured feedback and workplace related assessments (at least four times per year) and documented in a central e-logbook during the entire training period.

The curriculum allows a maximum of 1 year of training at an accredited training center for Prevention Medicine and Public Health, or in Clinical Pharmacology and Toxicology. Equally, 1 year research as part of an MD/PhD program, or under the supervision of a certified study sponsor-investigator outside of a training center for Pharmaceutical Medicine is accepted. No more than 1.5 years of training outside of Switzerland can be accounted for the curriculum. However, mutual recognition of foreign specialty titles in Pharmaceutical Medicine exists for countries with a similar training profile (e.g., Faculty of Pharmaceutical Medicine, 2018).

Currently, board examination consists of an extensive knowledge test (120 questions, multiple choice) followed by an assessment based on a written essay on three open formulated questions (2 h) and an interview based discussion (approx. 1 h) covering a published clinical research paper as well as other topics of Pharmaceutical Medicine. Under exceptional circumstances, a specialist title can be granted based on merits due to pioneering work in the field of Pharmaceutical Medicine.

A board-certified specialist has an obligation to complete 80 h of continuous medical education (CME) per year. Of these at least 50 h need to be testified through CME credits, of which half need to be in the field of Pharmaceutical Medicine. Importantly, CME credits in any other specialty can be recognized, if it is linked to the therapeutic field of daily work (e.g., CME in cardiology if involved in medicinal product development in cardiovascular diseases). CME credits must be self-recorded in an online system operated by the SIWF and completion of above mentioned requirements need to be certified periodically in 3 year intervals (Swiss Institute for Post-Graduate Training and Continuous Education, 2018a).

TRENDS IN PHARMACEUTICAL MEDICINE TRAINING IN SWITZERLAND DURING THE PAST 20 YEARS

Over the past 20 years, more than 120 physicians have been board-certified in Pharmaceutical Medicine (**Supplementary Figure S3**). The average number of physicians completing their training fluctuated around three to five per year. Only at time of introduction of this specialty title (1999–2003), a higher number of physicians working already in the field of pharmaceutical

medicine were certified based on their "merits" or through mutual recognition programs.

Initially, most specialists have been trained in industry, however, over the past 10 years there has been a surge in specialists trained at academic centers (**Supplementary Figure S4**). This coincides with the emergence of clinical trial units (CTUs) at university hospitals and other tertiary care centers, followed by the establishment of the Swiss Clinical Trial Organization (SCTO) in 2009 with the concomitant improvement of clinical trial quality and metrics (Von Niederhäusern et al., 2018). The number of certified training centers for Pharmaceutical Medicine based in the academic setting in Switzerland increased during this period from one to three.

At the same time, the number of certified training centers among the local affiliates of pharmaceutical companies declined in Switzerland. This can be attributed to two key reasons: First, a decline of physicians who select industry (and especially local medical affairs departments of pharmaceutical company affiliates in Switzerland) as a workplace for their post-graduate training. The absence of a trainee for more than 3 years leads to suspension of the training center certification. Second, several training centers lost their accreditation despite the presence of potential training candidates, because the head of the training center did not have the required qualifications. Additionally, the trend for internationalization and fragmentation of the different functions (research and development, medical affairs, regulatory affairs, pharmacovigilance, patient access, medical information), where reporting and governance structures are no longer maintained at local level, increases complexity for country medical directors to prepare and maintain a vocational training concept according to the curriculum.

Several pharmaceutical companies have their international head quarters or large operating centers including research and development, or medical affairs organizations based in Switzerland. Despite substantial investment in training and mentoring of employees, none of these are certified sites for vocational training. Administrative hurdles and constraints imposed by the Swiss post-graduate training process for physicians together with a lack of corporate interest and perceived benefit have anecdotally been quoted as reasons not to pursue.

EVOLUTION TO A COMPETENCY-BASED TRAINING CURRICULUM FOR PHARMACEUTICAL MEDICINE IN SWITZERLAND

The training curriculum itself is also subject to a regular accreditation process according to the Swiss Medical Professions Act. This was most recently conducted between February 2016 and August 2018. It involved a critical self-reflection on the purpose and content of the post-graduate training curriculum through the SSPM, as well as an external review by independent international experts. During this process we identified the need to further evolve the original knowledge based curriculum with "learning based" to a competency- based approach, aligned with the updated IFAPP syllabus and competency statement (IFAPP, 2016). Accreditation was granted and an updated curriculum has to be in place by end of 2019, which addresses the following additional requirements (Federal Office of Public Health, 2018a):

(a) A vision and mission statement has to be defined, which outlines the role of a specialist in Pharmaceutical Medicine and his or her interactions with other stakeholders of the healthcare system regarding to contribution of care.
(b) A plan or method to maintain the high quality of training in order to react and adapt to the evolving environment in healthcare.

The SSPM has established a new working group involving the heads of selected training centers to update the training curriculum through a series of workshops and off-line review cycles. Here we outline the core aspects of the revised curriculum and share the proposed changes.

The Role of the Specialist in Pharmaceutical Medicine in the Swiss Healthcare System

As a medical-scientific discipline, our vision is to provide the best possible therapeutic coverage for the benefit of patients and society through a medical need-based development and optimal use of medicinal products. The role of the specialist in Pharmaceutical Medicine is to closely collaborate with various stakeholders of the healthcare system in the context of the discovery, research, development and approval of new medicinal products, as well as safe and effective use of new and established medicinal products in daily clinical practice. The patient-centric, evidence-based decision process has a direct influence on the therapeutic coverage of patients, potentially beyond our national healthcare system.

A patient-centric development of medicinal products has to adhere to stringent legal, ethical and qualitative requirements with regards to the planning and conduct of clinical trials, accurate interpretation of pre-clinical, toxicological, pharmacological and clinical results with appropriate consideration of the benefit-risk profile and socio-economic aspects. The knowledge and competence in preparing documents for regulatory (e.g., clinical trial applications, marketing authorization application, periodic safety update reports) or reimbursement (e.g., health technology assessments) submissions, the continuous improvement of therapeutic benefit through appropriate medical information, supply coverage, appropriate risk management through the whole lifecycle of medicinal products requires expertise in Pharmaceutical Medicine. Therefore, the work of specialists in Pharmaceutical Medicine is valuable:

- In translational medicine and clinical research at academic centers and hospitals (incl. dedicated CTUs and general clinical services).

- At manufacturers and distributors of pharmaceutical or biomedical products and their service providers (including contract research organizations and consultancies).
- With regulatory and related competent authorities (e.g., Swissmedic, Federal Office of Public Health).

Revision to the Curriculum Structure

While the general structure of post-graduate training will remain the same (**Figure 1**), we propose a few procedural changes to strengthen the medical-scientific character of our discipline. A university-based post-graduate course with the completion of the Basis Diploma in Pharmaceutical Medicine according to the IMI/PharmaTrain syllabus (min 30 ECTS) (PharmaTrain, 2018) shall become the standard. We believe that peer-to-peer learning and exchange with colleagues from other areas of Pharmaceutical Medicine provide additional value over purely internal courses at training sites. In addition it aligns with the structure of the PharmaTrain Specialist in Medicines Development Certification Program (PharmaTrain, 2014).

The requirement for publication of an individual scientific or clinical research work in a peer-reviewed journal for the board-certification is currently debated. While the competency of medical writing (including assessments for medical information and preparation of regulatory documents) is being well trained at the centers, there is often limited opportunity to conduct original research. To improve scientific exchange we intend to mandate the participation in at least one meeting co-organized by the SSPM during the time of the specialist training. These meetings include the Annual Symposium in Pharmaceutical Medicine co-sponsored with the Swiss Association of Pharmaceutical Professionals (SwAPP), a 1 day event with state-of-the-art lectures and discussions on current topics, or the annual Spring Meeting organized by the Swiss Society of Pharmacology and Toxicology (SSPT). The SSPT is the umbrella organization of several scientific societies in this field. The aim of this 1 day event is sharing original scientific work, where active contribution is additionally incentivized through awards.

Finally, we would like to pursue the idea of an "exchange" program, where all trainees meet regularly for joint sessions and rotate among the affiliated training centers. During these half-day workshops, the trainee(s) elaborate one or more specific case studies under the supervision of the training head of the hosting center. The aim of such sessions would be to share practice and working experience between the different types of centers (e.g., academia- industry).

Defining the Swiss Catalog of Core Competencies in Pharmaceutical Medicine (SC^3-PM)

During the recent accreditation process we have proposed to evolve the current knowledge based curriculum to a competency based curriculum. Therefore we are preparing a Swiss Catalog of Core Competencies in Pharmaceutical Medicine (SC^3-PM) which adopts the concept of the IFAPP core competency description based on applied knowledge, skills and behaviors: We are currently adapting the proposed content in the domains of (1) Discovery of Medicines and Early Development, (2) Clinical Development and Clinical Trials, (3) Medicines Regulation, (4) Drug Safety Surveillance, (5) Ethics and Subject Protection, (6) Socio-Economics of the Healthcare System, and (7) Communication and Management (**Table 1**). Although refinement is still in progress, we would like to share already some of the thoughts and feedback received so far as part of the initial consultation:

TABLE 1 | Proposed competency statements for a specialist in pharmaceutical medicine (SPM) in Switzerland.

Domain	Core competency statements
(1) Discovery of medicines and early development	The SPM is able to identify unmet therapeutic needs, evaluate the evidence for a new candidate for clinical development and design a Clinical Development Plan (CDP) for a Target Product Profile (TPP).
(2) Clinical development and clinical trials	The SPM is able to design, execute and evaluate exploratory and confirmatory clinical trials and prepare manuscripts or reports for publication and regulatory submissions.
(3) Medicines regulation	The SPM is able to interpret effectively the regulatory requirements for the clinical development of a new drug through the product life-cycle to ensure its appropriate therapeutic use and proper risk management
(4) Drug safety surveillance	The SPM is able to evaluate the choice, application and analysis of post-authorization surveillance methods to meet the requirements of national/international agencies for proper information and risk minimization to patients and clinical trial subjects.
(5) Ethics and subject protection	The SPM is able to combine the principles of clinical research and business ethics for the conduct of clinical trials and commercial operations within the organization.
(6) Socio-economics of the healthcare system	The SPM is able to appraise the reasonable development and use of diagnostic, prophylactic and therapeutic means for the care of healthy volunteers and patients, thereby promoting the efficient use of available resources within the legal boundaries.
(7) Communication and management	The SPM is able to use the required skills for effective communication and management across stakeholders of the healthcare system, including clinical setting (e.g., patients, care givers, prescribers), competent authorities and interdisciplinary teams at the workplace.

(a) The current IFAPP statements focus on specialists (including non-physicians) working mainly on drug development in industry. However, we are convinced that the competencies have to equally apply to physician specialists working in academic institutes or regulatory

bodies. Hence, we are removing or replacing industry specific aspects to reflect the broader scope. Particularly competencies on commercial aspects shall be substituted by a more socio-economic view on the healthcare system, while business specific expertise can be acquired through other post-graduate programs (e.g., Master of Business Administration).

(b) We propose some revisions to better reflect the current issues and topics beyond development of medicinal products. Especially aspects on the competencies of a specialist in Pharmaceutical Medicine to enable access to medicines have been suggested. This includes expected knowledge, skills and behaviors with respect to health technology assessments and reimbursement. It also refers to situations, where supply of medicines could be limited or interrupted for various reasons. Further, we consider strengthening the aspect of medical information and appropriate communication with stakeholders along the whole lifecycle of a medicinal product.

(c) Ensuring compliance with Swiss law and regulations where appropriate.

CHALLENGES, PLAN OF ACTION, LEARNINGS AND OUTLOOK

A defined post-graduate training path and qualification process for physicians in Switzerland to obtain a recognized specialty title in Pharmaceutical Medicine has become well established in the course of the past 20 years. This has also recently been validated by the FOPH's re-accreditation process (Federal Office of Public Health, 2018a). However, this requires adherence to the general framework and certain operational aspects of post-graduate training for all physicians in Switzerland. While the concept for competency-based training was introduced by the SIWF several years ago within the overarching ordinance for physician post-graduate training, the IFAPP model now helps us to better define targets for applied knowledge, skills and behaviors regarding Pharmaceutical Medicine. Moving forward, we believe that the currently defined tools [Mini-Clinical Evaluation Exercise (Mini-CEX) and Direct Observation of Procedural Skills (DOPS)] can be adapted and adequately used for the required quarterly evaluation of the training progress and acquired competencies (Swiss Institute for Post-Graduate Training and Continuous Education, 2019b). At this stage we see limited opportunities to deviate from the defined structures for the final board examinations, other than possible adaptations in the questions to further explore competencies in the dimensions of "skills" and "behaviors." We will also continue to implement the structure and methodology provided by the SIWF for evaluation and documentation of competencies as part of the continuous professional development (Swiss Institute for Post-Graduate Training and Continuous Education, 2019a).

Drug development and lifecycle management of both, new and established medicinal products is a multidisciplinary endeavor involving professionals with different educational background in life sciences. The Swiss Association for Pharmaceutical Professionals (SwAPP) provides to non-physicians a similar 5-year certification program in Pharmaceutical Medicine following the IFAPP/Pharmatrain syllabus (Swiss Association of Pharmaceutical Professionals, 2019). Despite comparable expertise, certain clinical trial related activities (e.g., clinical investigator) are restricted by law to trained physicians.

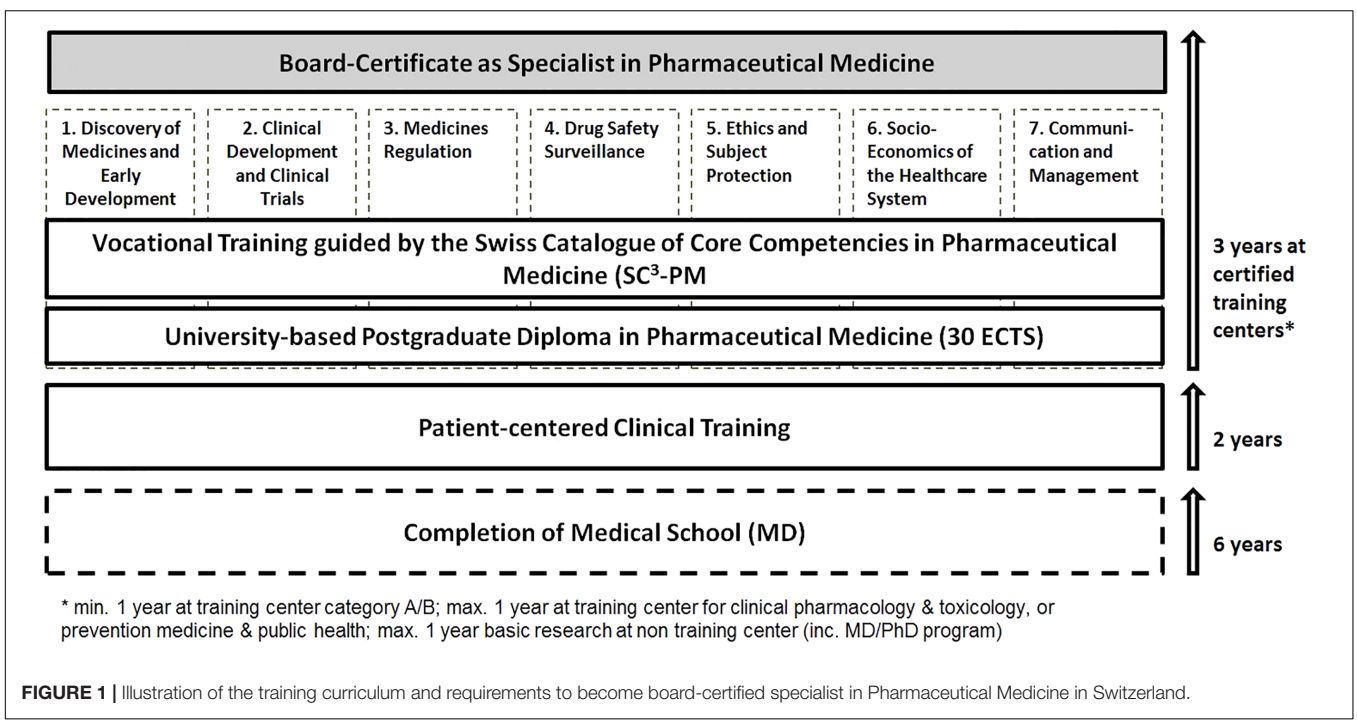

FIGURE 1 | Illustration of the training curriculum and requirements to become board-certified specialist in Pharmaceutical Medicine in Switzerland.

As a result of the accreditation process described initially, the SSPM has formed a working group with the heads of selected training centers to ensure regular exchange and dialog with the aim to improve objectives and quality of the vocational training across the different sites. We also intend to leverage areas of special interest and expertise of the various centers to allow for better exchange and peer-to-peer learning through rotation programs for trainees. Furthermore, this working group will serve as a platform to address evolving training needs and adaptation of the curriculum, namely for emerging trends such as personalized healthcare, big data and artificial intelligence, as well as to address new therapeutic approaches using gene-editing technologies. Most importantly, we are on track for timely implementation of this a new competency-based training curriculum for Pharmaceutical Medicine in Switzerland to build up the next generation of specialists.

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GS and MT prepared a first draft. All authors actively contributed in review and finalization of the manuscript.

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International Perception of Competence, Education, and Training Needs Among Biomedical Professionals Involved in Medicines Development

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The development of new medicines today, requires a multi-professional workforce, both in industry and the clinical research arena. Pharmaceutical physicians (PPs) and medicines development scientists (MDS) need a certain level of competence, achieved through on-the-job experience, with a postgraduate education foundation and continuous professional development programs. In order to assess the self-perception of competence, education and training needs, an on-line questionnaire based on the seven domains of competence, developed by IFAPP-PharmaTrain, was prepared and distributed among PPs and MDS members of IFAPP's affiliated professional associations in countries with facilities for postgraduate education. The data collection was run over a fixed period of three months in Japan, Italy, Brazil, and Spain during 2017. Results indicate low but variable levels of perceived competence for the various domains as well as seniority in the job. All respondents declared a significant need for continuing professional development in all domains. These results corroborate and support the continuous efforts, put in place by IFAPP and the PharmaTrain Federation, to foster the development of accredited education and training among professionals involved in medicines development.

Keywords: competence, education, training, pharmaceutical physicians, medicines development, IFAPP, pharmatrain, pharmaceutical medicine

INTRODUCTION

For some time now, the biopharmaceutical industry has been the key link between basic biomedical discovery and the emergence of novel medicines that prolong or improve life. However, the industry faces several ongoing and emerging challenges, including technical knowledge gaps, limitations in clinical testing, lowered productivity, higher development costs, increased regulatory requirements, growing payer pressures and patent expiration.

The lack of an adequately sized and appropriately trained multi-professional workforce, both in the industry and the clinical research field, is also a significant part of the problem. There is a perceived mismatch between the profiles and abilities of graduates from academic programs in healthcare professions, and the changing needs of the various health systems around the world. As a possible solution to achieving a transformative learning, an outcomes-based education, or competency-based education (CBE), has been proposed (Silva et al., 2013). Competent professionals would be able to perform their specific responsibilities effectively, such as bringing and maintaining new medicines to the marketplace. A need for competency-based education and training has been identified in the United States, Europe, and Latin America (Dubois et al., 2016).

These respective professional groups have been left with the responsibility to define the competencies needed to perform their function effectively. Competencies can be clustered in domains and can be learned through proper postgraduate education or continuing professional development (CPD) (Sonstein et al., 2014).

The International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)[1] and the PharmaTrain Federation (PharmaTrain)[2] assumed the task of producing the defined core competencies to orientate Pharmaceutical Medicine and Medicines Development as a discipline and profession. Three areas, seven domains and 57 core competencies at the cognitive level, were identified (Silva et al., 2013). The domains have been summarized in a Statement of Competence.

In addition to serving as a template for job profiles and portfolios, the domains can be used to identify general education and training needs. Based on these premises, an international survey among members of the IFAPP national member association was designed using an online questionnaire. Stakeholders were asked about their self-perception of competence and the need for education and training. The results were then assessed to identify gaps, in order to address the potential need for future development of pharmaceutical physicians and medicines development scientists.

MATERIALS AND METHODS

Development of On-Line Questionnaire

The questionnaire was developed based on the previously defined domains for competence in medicines development (Silva et al., 2013). An invitation to participate in the survey was sent to a defined list of members and non-members of the pharmaceutical medicine national associations in Brazil, Japan, Spain, and Italy. The responders who agreed to participate in this survey were asked for their demographic data (functional area, place of employment, level of experience, association with IFAPP's national member association) and their self-assessment of each of the seven domains for core professional competence. For each domain, the responders were asked their competence level (level-1 as "fundamental awareness" (basic awareness) to level-5 as "expert"), and its significance to their position (from "very low" to "very high"), in a Likert Scale as well as their training needs (Yes/No). The survey was conducted in an anonymous manner.

Responders were provided with a statement of competence defined by IFAPP, as well as a short description of each domain, to help their understanding of these as referred to in the survey. All questions and multiple-choice answers were developed using the Google on-line questionnaire format.

Definition of the domains (IFAPP-PharmaTrain Federation Collaboration Working Group, 2016) was used as per the following statement of competence.

Domain 1: Discovery of Medicines and Early Development

The Pharmaceutical Physician / Medicines Development Scientist can identify unmet therapeutic needs, evaluate the evidence for a new candidate for clinical development and design a Clinical Development Plan for a Target Product Profile.

Domain 2: Clinical Development and Clinical Trials

The Pharmaceutical Physician / Medicines Development Scientist can design, execute and evaluate exploratory and confirmatory clinical trials and prepare manuscripts or reports for publication and regulatory submissions.

Domain 3: Medicines Regulation

The Pharmaceutical Physician / Medicines Development Scientist can interpret effectively the regulatory requirements for the clinical development of a new drug through the product life-cycle to ensure its appropriate therapeutic use and proper risk management.

Domain 4: Drug Safety Surveillance

The Pharmaceutical Physician / Medicines Development Scientist can evaluate the choice, application and analysis of post-authorization surveillance methods to meet the requirements of national/international agencies for proper information and risk minimization to patients and clinical trial subjects.

Domain 5: Ethics and Subject Protection

The Pharmaceutical Physician / Medicines Development Scientist can combine the principles of clinical research and business ethics for the conduct of clinical trials and commercial operations within the organization.

Domain 6: Healthcare Marketplace

The Pharmaceutical Physician / Medicines Development Scientist can appraise the pharmaceutical business activities in the healthcare environment to ensure that they remain appropriate, ethical and legal to keep the welfare of patients and

[1] http://ifapp.org/

[2] https://www.pharmatrain.eu/

subjects at the forefront of decision making in the promotion of medicines and design of clinical trials.

Domain 7: Communication and Management

The Pharmaceutical Physician / Medicines Development Scientist can interpret the principles and practices of people management and leadership, using effective communication techniques and interpersonal skills to influence key stakeholders and achieve the scientific and business objectives.

Target Population

To maximize the participation from expected stakeholders in medicines development, a standard letter to explain the objectives of this survey was distributed by the IFAPP's national member associations in the above-mentioned countries. In addition, the questionnaire was posted on the IFAPP website to encourage individual participation from other member associations as well as for those possible responders not affiliated to IFAPP national member associations.

Study Period

Each national member association posted the questionnaire for three months. The questionnaire was first posted on-line in Japan (started on February 27th and terminated on May 31st, 2017), followed by Italy, Spain, and Brazil. During the posted period, representatives of the national member associations sent out reminder e-mails to their members to encourage participation. By the end of November 2017, the entire survey was completed, and the responses were analyzed.

Statistical Analysis Methods

The results for the perception of "competency level" included combined responses of 1, 2, and 3 from the competence level as a composite score of "0" (i.e., "less than competent"), and translated combined responses of 4 or 5 into a composite score of "1" (i.e., "competent"). This scale was also used for perceived "significance to one's position." For the questions regarding the "training need" per domain, "1" indicated "yes" and "0" indicated "no."

RESULTS

Responses for Analysis

In total, 680 full responses were obtained in this global survey. The number of responses were 388 in Japan, 194 in Italy, 61 in Spain, and 34 in Brazil. From the open survey posted on the IFAPP website, individual responses were sent from Korea, Philippines and Greece (one response each).

Demographics of the Respondents

Overall demographics of the respondents are shown in **Supplementary Table S1**.

Overall Statistics

The 46% of the respondents were working in clinical research, followed by medical affairs (11%). When classified by the place of employment, 54% of the respondents were working in sponsor organizations (pharmaceutical company / biotech company), followed by contract research organizations (CROs-26%). In terms of their level of experience, the majority had over 10 years of experience except in Japan, half of whom had less than 10 years of experience. Most Japanese respondents were from clinical research, whereas more medical affairs respondents were from Italy.

Functional Areas and Level of Experience

As the number of responses obtained from nine different functional areas were not evenly distributed, respondents were divided into six main categories according to their functional areas: clinical research, clinical operations and data management, regulatory affairs and safety, medical affairs and business development, overall management and others in consideration of the similarity in knowledge, skill and attitudes required in their functional areas. Less experienced respondents (less than 10 years) were found in the medical affairs and business development areas (**Figure 1**). On the contrary, most respondents involved in overall management had over 10 years of experience. With regards to national differences, most respondents from clinical research and medical affairs had over 10 years' experience across all countries.

Place of Employment and Level of Experience

Most respondents in sponsor organizations (69%) had over 10 years of experience, compared the experience of those working for CROs (56% reported less than 10 years). The proportion of respondents in management positions was somewhat similar: 9% in sponsor organization and 6% in CROs.

Overall Results of Competency Level, Significance to One's Position, and Training Needs Related to Domains

Survey responses concerning competence level, significance to position, and training needs are shown in **Figure 2**. The perception of competence varied among domains, though did not exceed 50% for any of them. A similar response, related to relevance to the job, was also found. Domains 2, 5, and 7 shared relatively higher rates in competence level and significance to their position, suggesting a close relevance between these two perceptions. In contrast to approximately 30% of respondents who felt less competent, and the significance to their position, high training needs (nearly 70%) was reported in all domains. In relation to the number of years of experience, less experienced respondents perceived higher training needs.

When compared across the seven domains of competencies, a higher perception of competence level and significance to their position were observed in functional areas related to medical affairs and business development, followed by regulatory affairs and safety. In clinical development related areas (clinical research, clinical operation, and data management), a perception of competence and significance to their position, were relatively lower in matching domains 1 and 2.

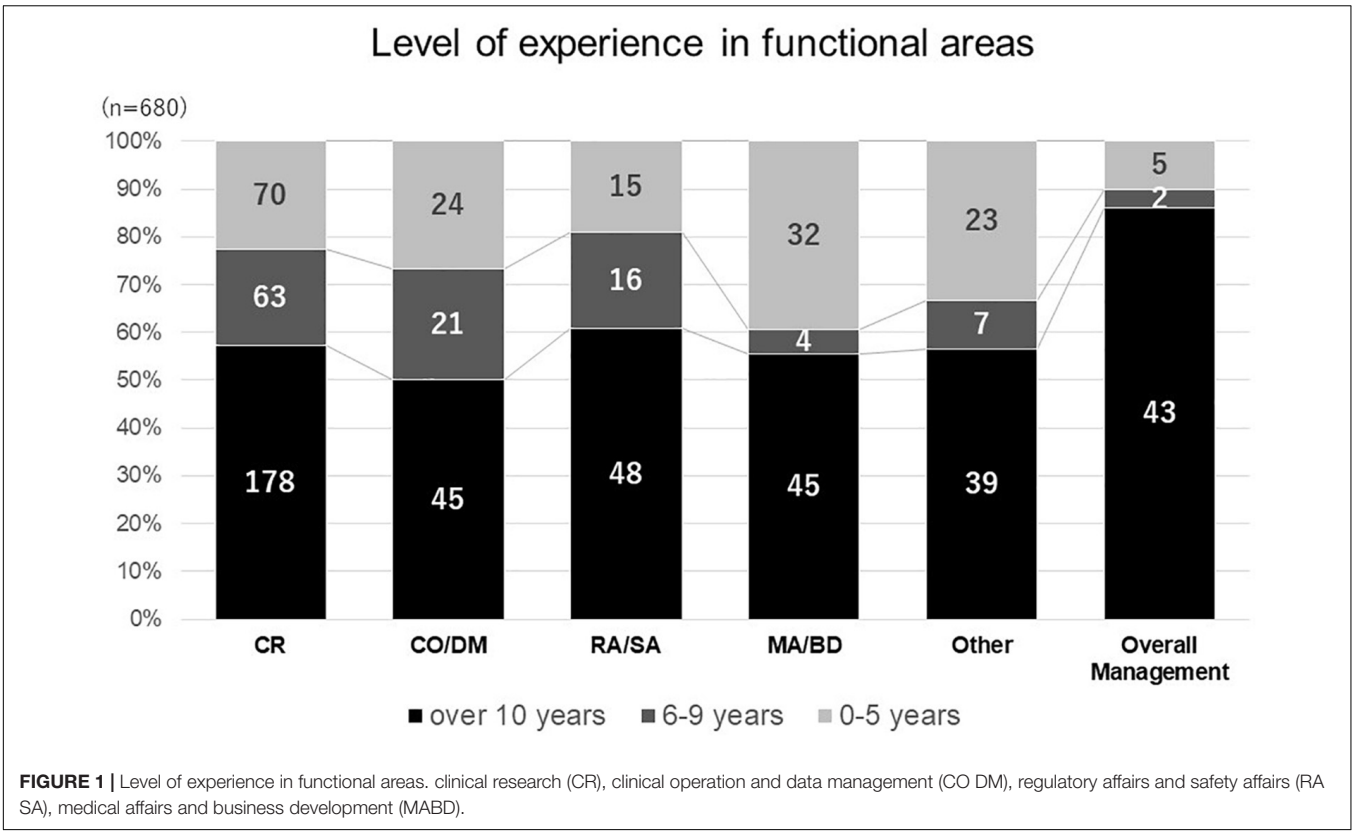

FIGURE 1 | Level of experience in functional areas. clinical research (CR), clinical operation and data management (CO DM), regulatory affairs and safety affairs (RA SA), medical affairs and business development (MABD).

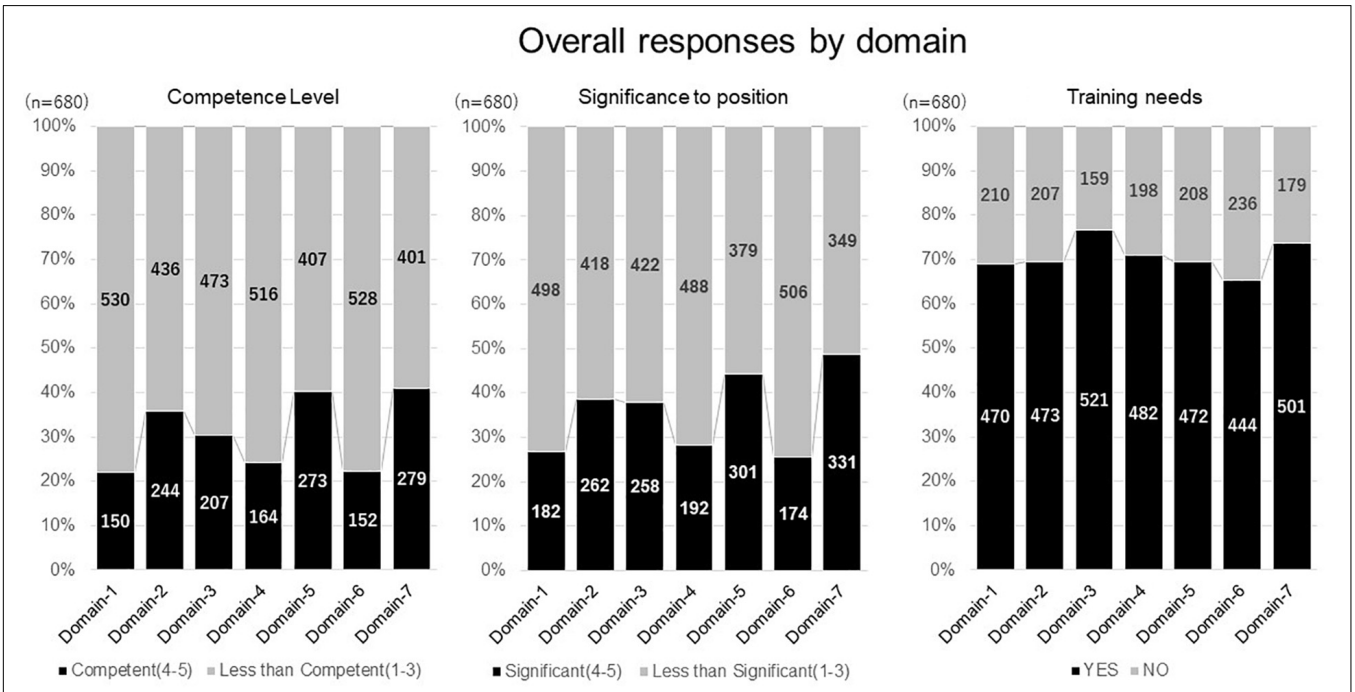

FIGURE 2 | Overall responses by domain. Domain-1: Discovery of Medicines and Early Development, Domain-2: Clinical Development and Clinical Trials, Domain-3: Medicines Regulation, Domain-4: Drug Safety Surveillance, Domain-5: Ethics and Subject Protection, Domain-6: Healthcare Marketplace, Domain-7: Communication and Management.

DISCUSSION

The need and value of competency-based education and training has become internationally recognized in a variety of fields, from an economic viewpoint and a broader social perspective (OECD, 2005). In the pharmaceutical industry, cognitive education has been structured and delivered in accordance with the standardized syllabus and core curriculum and promoted by the IFAPP and PharmaTrain. On-line educational programs in pharmaceutical medicine and medical affairs has also been developed by the IFAPP Academy[3], created as the educational arm of IFAPP, as a strategic collaboration with King's College London[4]. Recently, the IFAPP and PharmaTrain defined core competencies (Silva et al., 2013; IFAPP-PharmaTrain Federation Collaboration Working Group, 2016), according to which this survey was conducted, to seek stakeholders' view of the current status of competency-based education in this profession.

With regards to study limitations, which may have affected the generalizability of our observations, we missed responses from major countries active in medicines development such as the United States and United Kingdom. Secondly, the majority of responses came from highly experienced professionals in clinical development related functional areas, employed by sponsor organizations and CROs, which made a comparative analysis difficult. Thirdly, since the study was designed based on a non-probabilistic sample, as one single observation with different sizes for the national cohorts, analysis of the results requires caution. For example, more than half of the responses recorded came from Japan, where the culture of professional development and hiring opportunities differ from the other three countries. As a result, the overall respondents in medical affairs and business development appeared relatively less experienced due to proportionately more Japanese respondents (**Figure 1**), where the hiring of pharmaceutical physicians and medicines development scientists is a rather new area and possibly attracts relatively less experienced persons. Last but not least, the overall perception of competence was generally lower than 50% across the domains and precluded further analysis.

In terms of the common observations obtained within the limits, the overall analysis showed that the level of perceived competence in clinical development related domains (1 and 2) was lower in those working in CROs, compared to those working in sponsor organizations. As clinical development tasks are increasingly outsourced to CROs, their training should be considered in order to improve overall performance in medicines development. A high interest in training was also observed in all four participating countries across the domains, despite the relatively longer years of working experiences of the respondents, suggesting that this could be considered a global need. Industrial restructuring could be partially attributable to the loss of resources from workplaces, such as experienced mentors and the educational budget, as well as a changing environment for medicines development which requires new competencies in diverse areas. It should be noted that a similar study of a larger sample, contributed to by clinical research professionals from all over the world showed comparable findings, with significant variations among the respondents' perceived competence and relevance of domains and competencies as well as training needs for the various professional roles involved in clinical trials (Sonstein et al., 2016).

The results are indicative of the need for a more thorough confirmation on a country-by-country basis and a call for attention to all stakeholders. To promote competency-based education and training in a real-world setting, development of standardized assessment tools may add value. As the concept of Entrustable Professional Activities (EPA) has been adopted in a variety of areas of professional education, notably in medicine (Cate, 2013) and pharmacy (Pittenger et al., 2016), having a common currency for training may help to create a common understanding among stakeholders as well as mutual recognition of training offered by a variety of providers, as is proposed for residency training (Englander et al., 2014).

In summary, missing areas and opportunities for education and training can be identified in national surveys using the common definition of competencies and compared based on the understanding of the differences in cultural backgrounds and job markets. Opportunities for improvement could be provided with a standardized assessment in order to meet the expected level of competence for professionals in pharmaceutical medicine and medicines development.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

KI, TT, and HS contributed substantial to conceived and designed the work, analyzed and interpreted the data. KI, HS, DC, GK, and AJ collected the data and the reviewed the manuscript. PS and HS revised the work critically for important intellectual content. All authors provided final approval of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.00188/full#supplementary-material

[3]https://ifappacademy.org/

[4]https://www.kcl.ac.uk/index.aspx

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frontiers in Pharmacology

REVIEW
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Are Regulation and Innovation Priorities Serving Public Health Needs?

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A host of challenges confront healthcare authorities worldwide. Topping the list is the demand for innovative new medicines to treat a range of both infectious and non-communicable diseases, while containing spiraling healthcare costs. The challenge is particularly great in therapeutic areas where, despite significant medical need and economic impact, the technical challenges and commercial risk of development serve as disincentives to drug sponsors. These areas include cardiovascular diseases as well as diseases and disorders of the central nervous system. Currently, the development and approval of new active substances, with its disproportionate focus on oncology, is not in alignment with healthcare needs in most geographic regions. In this article, we discuss the origins of this misalignment and suggest various approaches to address healthcare needs going forward.

Keywords: new active substance (NAS), pharmaceutical R & D, innovation, drug development, regulatory agency

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ARE NEW ACTIVE SUBSTANCE LAUNCHES MEETING SOCIETY'S NEEDS?

Across the globe, spending on medicines as a percentage of overall healthcare expenditures ranges from 5 to 10% in most developed countries to as much as 60% in many emerging economies[1]. Despite the differences, healthcare systems are confronting the same dual challenges of controlling healthcare costs and the critical need for breakthrough treatments. Decision-makers must not only maintain adequate incentives for biomedical innovation, they must also ensure that the new medicines resulting from that innovation are accessible and affordable to patients who need them.

These challenges are increasing in scope and complexity as the world tackles what the World Health Organization (WHO) refers to as the "double burden of disease": i.e., the current crisis of emerging and re-emerging infectious disease epidemics and pandemics, and the growing impact of non-communicable diseases (NCD) on overall mortality and morbidity. Of 56.9 million global deaths in 2016, 40.5 million (71%) were due to NCDs: in particular, cardiovascular (CV) diseases (17.9 million, or 44% of all NCD deaths), cancers [9.0 million (22%)], and respiratory diseases, including asthma and chronic obstructive pulmonary disease [3.8 million (9%)]. Diabetes caused another 1.6 million deaths. Over three-quarters of NCD deaths—31.5 million—occurred in low- and middle-income countries, with about 46% of those deaths occurring in individuals 70 or younger (WHO, 2018). Currently, healthcare expenditures are an average of 4–5% of GDP in China and India—about half the amount spent in Western Europe and North America.

[1]*Adapted from The Pharmaceutical Industry and Global Health: Facts and Figures 2012*, International Federation of Pharmaceutical Manufacturers & Associations.

Compounding the challenge is the fact that whereas prescription drugs are often considered one of the most cost-effective forms of medical treatment, the worldwide output of New Active Substances (NAS: the first approval of novel drugs anywhere in the world) has been limited in the range of unmet medical needs being addressed; over the 5-year period 2013–2017, just two therapeutic areas—oncology and infectious diseases—have dominated NAS launches worldwide (**Figure 1**)[2].

ARE INDUSTRY TRENDS HELPING OR HURTING?

Oncology approvals have become dominant over the last decade. There has also been a surge in approvals in the infectious disease/vaccine (ID) area in recent years, due in part to heightened public awareness of global pandemics and antibiotic resistance. In contrast, approvals of new CV and central nervous system (CNS) agents have fallen far behind, a cause for concern for two reasons. The first is that these trends are not in sync with public healthcare needs. While cancer is certainly a major health issue, it is not the primary health concern in terms of mortality and morbidity; in the US and Western Europe, CV disease (CVD) is number one in overall mortality, and in many emerging and developed markets alike, CVD is associated with growing levels of morbidity and premature death. The second reason for concern is that the NAS approval trends run counter to the mission of national regulatory authorities. These authorities are tasked with addressing medical needs by dedicating energy and resources proportionate to the public health impact of the causative disease. When this is not done, agency decision-making on priorities and resource allocations should be re-evaluated, and recalibrated if necessary.

Current NAS approval trends are troubling in an additional context. While national regulatory authorities influence how many and how fast products reach the marketplace, it is the pharmaceutical industry that typically controls what types of drug candidates enter the development pipeline. The two therapeutic areas that have remained static in recent decades—CNS and CV—represent areas with substantial market potential. Mental health was tied with cancer as one of the four most costly medical conditions in the US during the decade of the 2000s, and the American Heart Association estimates that over a third of Americans currently suffer from some form of CVD. Worldwide, CVD is considered the fastest growing NCD health threat. For example, obesity has reached epidemic levels in some developing countries, as the populations have developed a growing penchant for western-style diets that pre-dispose to metabolic syndrome and its disease sequelae. In the CNS area, the WHO projects that by 2020, depression will be the second leading cause of disability worldwide (World Health Organization, 2004).

Despite the enormous market opportunity in the CV and CNS space, the number of NAS approvals in these areas is static or declining; CV and CNS combined equal only about half the number of oncology approvals in 2013–2017. Whereas, the recent dominance of oncology approvals is largely a US phenomenon (82% of oncology launches among global NASs from 2013 to 2017 were in the US), the facts that 58% of NASs worldwide originate in the US (148/256), and 47% of the worldwide pipeline is focused on oncology/immunology[3], highlight a global concern going forward.

It is worth noting that the growth in NAS launches of ID products (both therapeutic and prophylactic) represents a positive trend and suggests an alignment of private/public resources and public health needs. This trend is the result of two factors. The first is that ex-US output of NAS appears to have a better balance of therapeutic areas than that of the US (see **Figure 2**). The second factor is that the pipeline investment in ID drugs has benefitted from strong public health advocacy—a type of advocacy fundamentally different from the patient-focused advocacy spearheaded by cancer patient organizations, such as the American Cancer Society, and those of other disease areas.

One example of the striking effectiveness of public health advocacy in ID is the creation of the Generating Antibiotic Incentives Now (GAIN) Act in the US, which resulted from the efforts of a stakeholder group of 50 healthcare and labor organizations, who petitioned the US Congress to address public health needs in the area of antibiotic resistance[4]. The GAIN Act allows for the expedited review and approval of new ID drugs, as well as 5 years of market exclusivity. The Act's effectiveness was highlighted in a 2017 US Government report, crediting the legislation with achieving 101 ID designations and six approvals <5 years into the program (GAO-17-189, 2017). Going forward, however, success in bringing new ID drugs to market is not guaranteed; it is dependent on FDA resources and political will.

THE UP AND DOWN SIDES OF FACILITATED REGULATORY PATHWAYS

The regulatory environment can have a sizeable impact on the introduction of innovative new medicines, especially in areas with high unmet medical needs but low market incentives. Whereas, the ability to set high prices for new drugs, and extend market exclusivity, act as "pull" incentives, in that they increase the likelihood of sufficient return on investment and spur new research and development (R&D) activity, regulatory initiatives aimed at speeding development and review times serve as equally powerful "push" incentives, in that they lower the financial and logistical barriers to market entry, and reduce the technical risk of product development (Milne, 2014).

[2]Note that in **Figure 1**, Metabolic-Endocrine, which appears as the second most common NAS therapeutic area, represents a composite category of drugs for endocrine diseases (e.g., type 2 diabetes), metabolic diseases, and congenital enzyme deficiencies (including many orphan drugs for rare conditions).

[3]*Decline and Fall of the Pharma Pipeline*. (2017). No. 3847. Available online at: https://scrip.pharmaintelligence.informa.com/SC098394/The-Decline-And-Fall-Of-The-Pharma-Pipeline (Accessed December 4, 2018).

[4]*50 Organizations' Letter to Congress on the Urgent Need for New Antibiotics*. (2012). Available online at: https://dpeaflcio.org/wp-content/uploads/Antibiotics-Sign-On-Letter-022212-House-Version.pdf. (Accessed November 19, 2018).

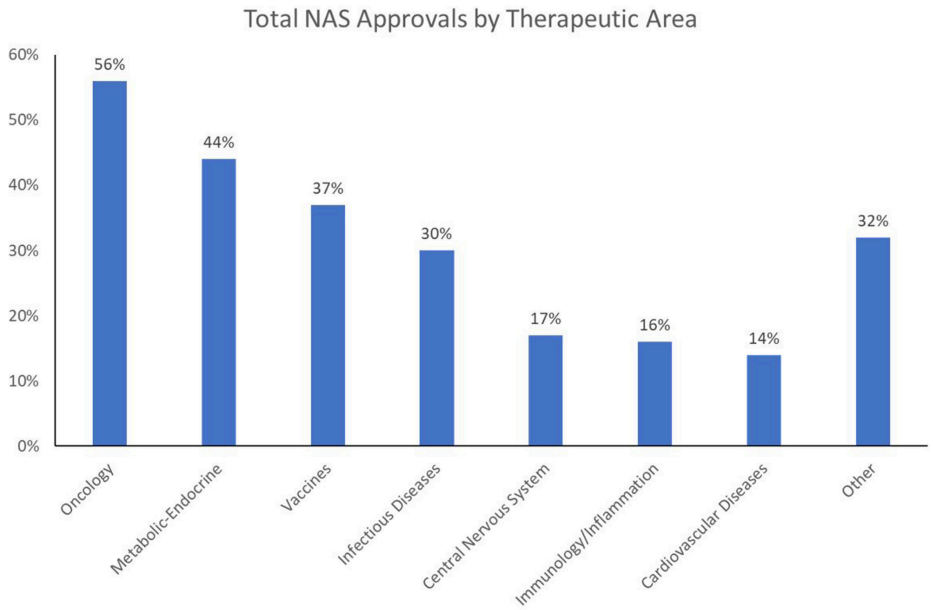

FIGURE 1 | 2013–2017 NAS approvals by therapeutic area.

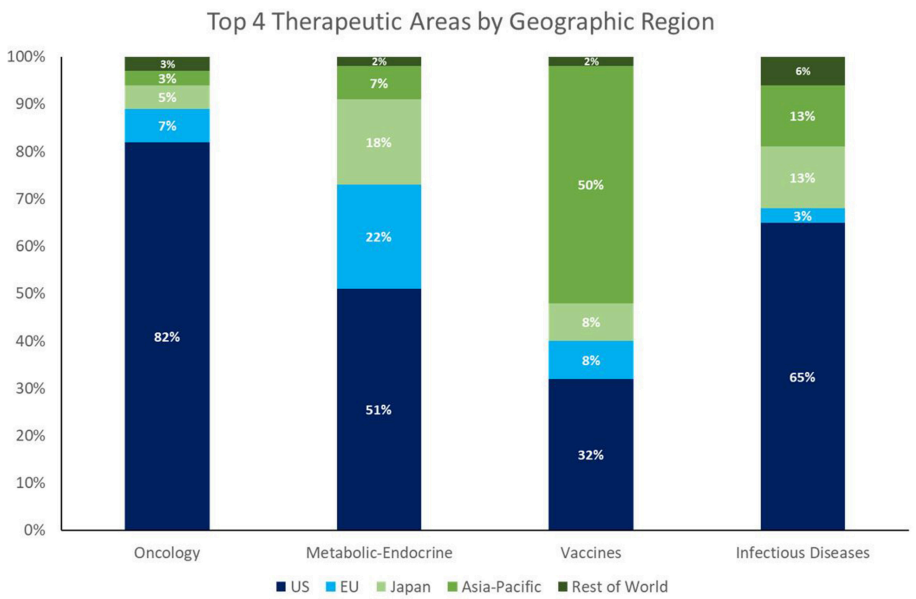

FIGURE 2 | 2013–2017 NAS, top 4 TAs by top 4 regions.

The US FDA employs a full panoply of what are referred to as Facilitated Regulatory Pathways (FRPs), including (a) priority review (submissions receive a 6-month review time, compared to a 10-month standard review), (b) accelerated approval (conditional approval based on surrogate, or indirect measures of benefit), (c) fast track designation (increased access to scientific interaction with the FDA and rolling reviews of portions of product applications as they become ready), and (d) breakthrough therapy designation (BTD: includes fast track designation incentives and "all hands on deck" collaborative, cross-disciplinary engagement by the FDA).

Since 2000, oncology drugs have received 45% of all FRPs awarded by the FDA, representing 32% of all priority reviews, 53% of all accelerated approvals, and 50% of all fast track designations (Milne, 2014). This has contributed to industry's growing focus on oncology R&D, which has no doubt benefited from the expansive scientific knowledge base that exists due to the US National Institutes of Health (NIH) and academic medical

centers' response in the 1970s to President Nixon's declaration of the "War on Cancer." To highlight the point, during the decades of the 1980s and the 1990s, when cancer discovery efforts were still germinating, oncology drugs only represented 5 and 12% of overall US new drug approvals, respectively. By the first decade of the 2000s, however, that number reached parity with CV drugs at 19%. And in the period 2010–17, oncology drugs represented 29% of new approvals, compared to 14% for ID drugs, and 12% each for CV and CNS drugs[5]. In sum, in recent years, oncology drugs have been a major beneficiary of FRPs, which has stimulated investment in oncology R&D.

Is there a downside to FRPs? It is worth remembering that regulatory oversight is, in many ways, a zero-sum game. Political will and public advocacy are often lacking to address unmet medical needs in certain critical areas, and resources at regulatory agencies are finite. The US FDA itself has opined that such imbalances can result in boosted performance in one area to the detriment of another, effectively "squeezing out" certain therapeutic areas. There is a critical need for open debate to ensure alignment of public policy with public health needs.

WHAT NEEDS TO BE DONE

Prioritization

Regional and national commissions should be created to review medical priorities, resource demands, and policy initiatives to achieve desired goals. Commissions should include experts from government, academia, industry, patient advocacy, insurers, and medical practice. The commissions should assess their region's immediate and long-term health needs and review the innovation landscape to determine whether current public and private R&D efforts are appropriately focused and funded.

Within regulatory authorities, FRP offices should be created to triage new drug applications. To help subsidize these activities, sponsors of candidate drugs could pay an application fee to the regulatory authority. If the FRP office determines that a drug candidate is eligible for one or more special regulatory programs, the sponsor would be exempt from paying any additional fees beyond standard user fees.

Emerging Sponsors

The new drug research and development landscape is shifting dramatically, from the dominance of traditional big pharma to the emergence of venture capital–backed smaller companies and "emerging sponsors," defined by the US FDA as the sponsor listed on the approval letter who is not a holder of a previously approved application. Sponsors are classified as "emerging" even if they have partnership or parent relationships with sponsors of a currently approved product. In recent years, ∼40% of new drug and biologic approvals in the US were from emerging sponsors (Jenkins, 2012). Emerging sponsors share many of the same characteristics as start-up companies, in that they may have little or no experience with commercial drug development, the regulatory process, or product launch. Pharmaprojects reports that of ∼4,000 pharmaceutical companies with active pipelines, 56% have just one or two products in the pipeline, tacitly qualifying them as emerging sponsors[c]. An FDA study documents that emerging sponsors are more likely to have multicycle reviews (DiMasi and Faden, 2009), and are less likely to garner approvals (50% approval rate as compared with 80% for medium/large companies) (Mathieu, 2013).

The relative lack of R&D experience of emerging sponsors highlights the need for institutional programs and courses that offer training in the drug development process. Several highly regarded programs currently exist, such as Tufts CSDD's Postgraduate Course in Clinical Pharmacology, Drug Development and Regulation; the IFAPP Academy-King's College London Medical Affairs in Medicines Development online course; the University of California: San Francisco's American Course in Drug Development and Regulatory Science; and the University of Basel's European Center for Pharmaceutical Medicine. These programs offer a broad yet comprehensive overview of the drug development and regulatory process.

New Technologies

Oncology R&D has benefitted greatly from dramatic advances in our understanding of the immunologic and genetic bases of cancer. A majority of recently approved cancer drugs are considered among the most innovative genomically-targeted precision medicines. In the US, much of the growth in scientific knowledge can be traced directly back to a high number of research grants awarded by the National Institutes of Health that focus on immunology and cancer.

Despite remarkable advances in the oncology field, it is worth asking: In light of the increasing availability of prognostic and diagnostic technology available for CNS disorders, and promising new approaches in regenerative medicine to treat CVD, is the continued dominance of oncology/immunology out of balance with health needs, both economically and medically? According to Pharmaprojects, nearly 50% of the global R&D pipeline is focused on anti-cancer therapies (4232/8934 products in 2017)[c]. Some observers have suggested that this over-emphasis on oncology in global R&D pipelines is a misallocation of resources and has generated a surplus of competition in some relatively narrow cancer indications. Moreover, the likelihood of success for oncology product development is relatively low. In a 2016 analysis, SCRIP Pharma Intelligence determined that immuno-oncology is one of the least successful therapeutic areas in terms of Phase III projects moving on to a regulatory filing, with only a 40% transition probability, compared to 58% for all ∼1,500 products included in the analysis (Lucy, 2016).

The US FDA, the EMA, and other national regulatory authorities have relied on regulatory science (i.e., developing new tools, standards, and approaches to assess safety, efficacy, quality, and performance) to understand and incorporate advances in new technologies. Nonetheless, challenges persist in agencies' attempts to integrate the risk-benefit profile of drugs, biologics, and devices during the product's entire time on the market. The goal is to close the evidence gap between the information regulators require to make decisions regarding product approval, and the type of information increasingly used by the medical

[5] *Unpublished Tufts CSDD Data*, Tufts CSDD Marketed Database, (2018).

community, payers, and others charged with making patient health care decisions.

Global Competition vs. Harmonization

Asia (arguably excluding Japan) has been one of the greatest beneficiaries of globalization. The region as a whole accounts for 40% of world trade, according to the 2017 BCG report *How Asia Can Win in the new Global Era*. Recently however, some shifts in global economic currents have become detectable. Although manufacturing will remain an important contributor to growth in Asia, export-led economic models are now under pressure in most of the region. One reason for the decline is that trade, whose contribution to global GDP grew from around 25% in the 1960s to more than 60% in 2008, has since stalled. Another factor is that Asia's previously enormous manufacturing cost advantages have shrunk, as wage growth has outpaced productivity (BCG Henderson Institute, 2017).

Nonetheless, with 60% of the world's population, the Asia-Pacific region is a significant focus for pharmaceutical sales by both domestic and foreign firms. The region also appears poised to become a nexus for pharmaceutical production, especially for vaccines and generics. However, Asian policymakers and companies cannot rely excessively on export manufacturing. To remain competitive in the global marketplace and to meet the needs of its own burgeoning population, Asia-Pacific must nurture innovation, such as regenerative medicine, in research areas that offer promising advances for unmet medical needs through international collaboration, strategic partnerships, and global harmonization.

Patient-Focused Drug Development

According to the US FDA, patient-focused drug development (PFDD) describes efforts to ensure that the review process benefits from a systematic approach to obtaining patient perspectives on disease severity and medical need. For example, in the CNS area, the FDA has proposed a new approach for Alzheimer's disease R&D that allows treatment of pre-symptomatic patients to slow the accumulation of substances in the body believed to be biomarkers of clinical disease, or to treat patients with early disease before functional impairment is apparent through an accelerated approval pathway on the basis of assessment of cognitive outcome alone. There is precedent for this type of PFDD from AIDS activism in the 1990s, during which the FDA and industry handled the risks through patient involvement in a meaningful process of informed consent (Powell, 2013).

For CNS drug development, in general, many major diseases and disorders may benefit from a PFDD approach. At a recent FDA meeting, patients with amyotrophic lateral sclerosis (ALS) argued emphatically that regulatory revamping is necessary to get research moving in the field, as there is only a single drug on the market for the disease (the orphan drug riluzole extends life of ALS patients by about 3 months). The ALS patients' recommendations were, in essence, a wish list for all unmet needs in CNS: (1) incentivize companies, in particular small companies that seem to populate this research area, by clarifying the regulatory pathway through guidance; (2) do not be overprotective of patients in terms of risk; (3) allow for abbreviated pre–investigational new drug toxicology testing; (4) permit the use of historical controls; (5) allow expanded access; (6) utilize accelerated approval; and (7) provide for a limited population designation under the guidance of supervising neurologists (Haley, 2013), as might occur under BTD.

Another condition that could benefit from a PFDD approach is obesity. The need was discussed at a George Washington University Stakeholder Panel in which it was suggested that obesity should be viewed as three conditions: obese but otherwise well; obese with risk factors; and obese and sick. In an Infectious Diseases Society of America approach, indications should be targeted to specific patient populations through Special Medical Use (SMU) designation to control off-label (and off-target) use, instead of risk evaluation and mitigation strategies (REMS), which were not designed for that purpose. Secondary end points should be added on the benefits side of the scale, such as effects on joint pain, urinary incontinence, sleep apnea, and mobility (Ferguson et al., 2013).

THE WAY FORWARD

National regulatory authorities worldwide are responsible for protecting and promoting public health, yet they must often expend energy and resources reacting to public health emergencies and political pressure. They must engage with an increasingly global pharmaceutical enterprise, deal with growing patient activism, and leverage new technologies and social media, all the while remaining cognizant of national cost-containment pressures. Unfortunately, whereas the challenges have grown, the resources available to deal with them have remained the same or decreased. This disparity threatens to relegate the health problems that afflict the majority of patients at any given moment to secondary concerns. Innovation follows investment, and investors respond to the regulatory and economic climate. By continuing to emphasize PFDD, and by demonstrating regulatory flexibility in disease areas with high unmet need (beyond cancer, AIDS and orphan diseases), regulatory authorities can indirectly incentivize R&D in these important therapeutic areas.

There is no simple answer to how to stimulate innovation in therapeutic areas where the need is great but commercial incentives may be lacking. The solution requires a multi-stakeholder approach to identify demand and build consensus for change. Going forward, sponsors, regulators, policy makers, payers, academics, key opinion leaders, and, perhaps most importantly, patients, must work together to chart a course to a healthier future.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Creation of a Competent Global Regulatory Workforce

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Regulatory affairs professionals play pivotal roles in ensuring healthcare products adhere to regulations and in gaining regulatory approval for product manufacture and sales. To do this, they must understand the science and technology connected with a product, the company's business goals, and, most importantly, the nuances of national and international regulations and guidances connected to the product. But although they perform complicated work connected to the entire product development lifecycle, surveys have indicated only 14% of regulatory professionals come to the field with a degree related to the work and for more than half, regulatory work is a "second career." The net result is a heterogeneous professional population that must learn complex, detailed work on the fly in as short a time as possible. Without a structure to guide development, these expectations are a challenge for someone new to the field, that person's supervisor, and for training developers. Various non-profit groups have created competency models to provide this structure, but because competencies only identify traits demonstrated by high-performing professionals, not the specific tasks associated with individual roles, these models have had limited impact on the profession. Identifying and structuring actionable tasks based on a competency model would increase the model's utility, dissemination, and usage. Entrustable professional activities might provide the methodology for doing so.

Keywords: competency, competency model, entrustable professional activity, behavioral indicator, regulatory affairs, regulatory professional

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INTRODUCTION

Regulatory professionals working for healthcare product companies impact nearly all phases of a healthcare product's lifecycle as part of their work to gain and maintain regulatory approval. But although they share the common goal of ensuring product safety through regulatory compliance, incredible variations exist in the scope and responsibility of a regulatory professional's work, depending on company size, organization, product portfolio, and development timeline. Thus, a single regulatory professional may do any combination of the following:

- Contribute to creating the regulatory strategy related to a product's eventual approval, which requires a strong command of international regulatory authorities' regulations and guidances.
- Collaborate with product developmental teams, from working with engineers on a medical device in the design phase to researchers during the clinical phase to advertising teams in the promotion and labeling phase.
- Ensure adherence to manufacturing requirements, which can include guiding inspections of manufacturing facilities and coordinating the company's response to inspection results.

- Gather all materials generated in the research and development, preclinical or non-clinical, and clinical phases to create a submission packet for regulatory approval, then shepherding the application throughout the approval process.
- Monitor product for any post-approval changes that may impact the original approval parameters.
- Comply with requirements for periodic and annual reports and adverse event reporting.

Their participation is pivotal to a product ever receiving regulatory approval, so they must be involved in every stage, providing strategic, tactical, and operational direction and support for working within regulations to expedite a product's development and delivery (Regulatory Affairs Professionals Society, 2015). Despite this important role, few regulatory professionals come into the field directly from an undergraduate program and most come from a career in another field or profession.

Every 2 years, the Regulatory Affairs Professionals Society (RAPS) surveys regulatory professionals around the globe about their work settings, educational backgrounds, compensation levels, and other demographic and work information. In the 2018 study, 86% of 2305 respondents reported they had degrees in something besides regulatory affairs, and most respondents indicated they came to regulatory affairs after working in another profession, including quality assurance/quality control (18% of respondents), research and development (12%), life sciences research (7%), engineering (7%), and clinical research (5%) (Regulatory Affairs Professionals Society, 2018). The disparate backgrounds of regulatory professionals and their complex, varied roles in product development make it challenging to provide a "one size fits all" training and development solution. Competencies and competency models can provide a structure for their professional development by highlighting the "unique characteristics of the most successful or even outstanding" regulatory professionals, although using competencies to create development plans can be challenging (Graber and Rothwell, 2010).

REGULATORY COMPETENCY MODELS

Many groups have created competency models for regulatory professionals, including The Organization for Professional in Regulatory Affairs, or (The Organization for Professionals in Regulatory Affairs (TOPRA), 2018), the Association of Graduate Regulatory Educators, or (Association for Graduate Regulatory Educators (AGRE), 2014), and RAPS in 2013, and 2015. (Refer to **Table 1** for a comparison of regulatory professional competency models). RAPS's experience with developing and disseminating their frameworks highlights competency model potential benefits, but also shows their limitations and hints at ways in which their utility may be improved.

TABLE 1 | Comparing domain topics across five regulatory professional competency models.

Domain topic area	Professional development framework (RAPS, 2013)	Core competencies for graduates of MS programs in regulatory studies (AGRE, 2014)	Regulatory competency framework (RAPS, 2015)	Regulatory competency framework, updated (RAPS, 2018–2019)	Regulatory affairs competency framework (TOPRA, 2018)
General, foundational information	Knowledge, Skills, and Abilities Throughout the Product Lifecycle		Scientific and health concepts	Regulatory strategy and planning	Strategy and technical
Strategic planning	Strategic planning	Strategy	Regulatory frameworks and strategy	Regulatory strategy and planning	Strategy
Premarketing/preapproval	Premarketing	Regulations, clinical, quality	Product development and registration	Premarketing/Post-marketing	Technical
Post-marketing/post-approval	Post-marketing	Regulations	Post-approval/Post-market	Premarketing/Post-marketing	Technical
Communication and soft skills	Interfacing	Communication	Communication	Professional development	Communication
Leadership			Leadership	Management and leadership	Core
Business acumen	Strategy	Strategy	Business acumen	Professional development	Business and Organizational Awareness
Ethics			Ethics	Professional development	Core

THE REGULATORY AFFAIRS PROFESSIONAL DEVELOPMENT FRAMEWORK

In 1990, RAPS created the Regulatory Affairs Certification (RAC), based on job analyses of regulatory professionals with 3–5 years of experience. But although a solid step toward identifying the knowledge and skills of a competent regulatory professional, it did not fulfill the need for a "true" competency model because of its focus on a specific portion of a regulatory professional's career and on product lifecycle-related items.

Recognizing that the profession needed a more complete competency picture, in 2003 RAPS initiated work on developing a full competency model that would create a more holistic vision of the successful regulatory professional and identify how those competencies morphed through various stages in a professional's career. From 2003 to 2007, senior regulatory professionals representing different product sectors, professional positions, company structures, and geographic responsibilities created comprehensive outlines of a regulatory professional's practice and associated knowledge and skills at different career stages. Developers then validated those outlines through comprehensive surveys followed by a series of focus groups. By the end of the process, more than 500 regulatory professionals had participated in the development and validation processes over a 2-year period to create the Regulatory Affairs Professional Development Framework (PD Framework).

An early decision in development was that the PD Framework should be as universal as possible, which meant it would be:

- Role-agnostic, so it should be applicable for regulatory professionals in industry, government, research, clinical, and other settings.
- Product-agnostic, so it would not mention sector-specific regulatory processes.
- Region-agnostic, so it would not mention specific regulatory authorities or guidances.
- Role-agnostic, so it would not provide details related to a regulatory professional's specific knowledge, skills, or competencies.

PD Framework developers matrixed competencies along two dimensions: level and domain.

Level referred to four stages of a regulatory professional's career:

- Level I: New to the field. Comes to the position with professional skills, such as basic project management and communications, so must focus on learning regulatory frameworks, requirements, legislation, and processes.
- Level II: Builds on that foundation and by the end of Level II, should be familiar with all regulatory tasks connected with his or her company's product lifecycle and submission process. These expectations mirrored the items in the RAC exam outline's topics, so the logical expectation was that the professional should earn the RAC by the end of this level after roughly 5 years of experience.
- Level III: Transitions from working entirely at the tactical level into a role that leverages technical knowledge into strategy. Often, the professional also becomes a manager of lower level regulatory professionals.
- Level IV: Shifts almost completely out of direct tactical regulatory work to be strategic regulatory lead, which includes developing new approaches for achieving or defining business objectives that build on his or her strong understanding of regulatory requirements, opportunities, risks, and alternatives.

Domains were logical subdivisions within the professional's scope of responsibilities:

- Strategic planning, which included regulatory strategy-related work throughout the lifecycle, organization of regulatory information and knowledge, integration of regulatory perspectives into the organization, and regulatory policies and procedures.
- Premarketing, which included any regulatory work connected to the research and development, preclinical, and clinical phases through submission/registration.
- Post-marketing, which involved reporting, compliance, and post-market surveillance, as well as labeling, advertising, and promotion.
- Interfacing responsibilities extended throughout the lifecycle and included communication and interaction within the organization, with regulatory agencies, professional trade, standards organizations, and with other stakeholders.

Although developers didn't want the PD Framework model to provide granular details about a regulatory professional's work, they did include overviews of the knowledge, skills and abilities of the regulatory professional at each level by domain (Regulatory Affairs Professionals Society, 2007).

DEVELOPING THE REGULATORY COMPETENCY FRAMEWORK

By their nature, competency models identify the characteristics of excellent performance at a specific moment of time. As such, organizations must revisit them periodically to ensure accuracy (Graber and Rothwell, 2010). In 2015, RAPS staff and 15–20 subject matter experts, did this with the PD Framework and created the Regulatory Competency Framework (RCF). **Supplementary Material**: (Regulatory Affairs Professionals Society, 2015).

The largest difference between PD Framework and RCF was expansion from four domains to eight, in the hope that they would better represent both regulatory-specific and general professional competencies:

- Scientific and Health Concepts: Understanding and application of evolving basic and translational science, regulatory science and public health concepts to drive new approaches to improve the development, review, and oversight of healthcare products.

- Ethics: Ability to integrate and demonstrate core values, integrity, and accountability.
- Business Acumen: Ability to leverage systems and processes to successfully operate a regulatory function.
- Communication: Ability to clearly convey or exchange information with stakeholders within and outside the organization.
- Leadership: Ability to direct and contribute to initiatives within the organization, with groups engaged in developing good regulatory practice and policy, and within the regulatory profession. Ability to provide clarity and direction amid complexity and develop solutions for self, colleagues and the organization.
- Regulatory Frameworks and Strategy: Knowledge of regulatory frameworks and external environments and the ability to apply these to regulatory solutions throughout the product lifecycle.
- Product Development and Registration: Knowledge of the research and development, preclinical and clinical steps and related regulations in healthcare product development.
- Post-approval/Post-market: Knowledge of requirements and processes for maintaining a product on the market, reporting and surveillance (Regulatory Affairs Professionals Society, 2015).

UPDATING THE RCF

Although the RCF provided a solid competency model, data gathered in 2018 suggested challenges in its application. Based on surveys and education-related evaluations, over half of RAPS 16,000 members were aware of the RCF, but fewer than 100 individuals had downloaded the RCF from its 2015 release until late 2017. Furthermore, only a handful of companies had followed the RCF's recommendations of tailoring its general competencies to their specific products and organization. Instead, they used it to create position descriptions, which demonstrated a complete misunderstanding of how to use competency models (Graber and Rothwell, 2010). When asked why, respondents said consistently that the model "lacked real world applicability" because of its high-level overview and sector-agnostic approach.

The information led to a reassessment of the RCF. Reviewers agreed that the RCF needed improvements, like removing redundancies and addressing gaps in professional skill competencies, but decided to maintain the RCF's high-level, universal view of regulatory competencies. However, in recognition of comments about lack of applicability, they created additional tools to help individuals use the model.

Improvements to the RCF's content included the following:

- The Ethics domain both contained competencies better suited to other domains and failed to capture the ethics of regulatory work as elegantly as the preexisting RAPS Code of Ethics. **Supplementary Material**: RAPS Code of Ethics. As such, the updated RCF guided regulatory professionals to become familiar with that document and included only a few ethics-related competencies.
- Management competencies, such as developing subordinates and identifying team resource needs, added to existing competencies to create a Management and Leadership domain.
- Developers condensed the premarketing and post-marketing domains into one.
- They eliminated redundancies.
- Items from the Scientific and Health Concepts domain moved to Regulatory Strategy and Planning.
- The subject matter experts created a Professional Development domain to hold competencies that all professionals should develop, including items from the Business Acumen and Communication domains.

The greatest alteration in the updated RCF was that it would be not one, but three, tools:

- The RCF remained a high-level, universal vision of competencies evidenced by the most successful regulatory professional at all four career levels. Unlike the previous version, however, the update included more guidance on how to apply the competencies to an individual. The hope is that for many, the additional assistance will be sufficient.
- However, developers recognized that many people will need help interpreting the RCF's intentionally-broad competencies, so they created *behavioral indicators* to provide examples of behaviors that lead to achievement of the RCF competency. For example, a competency in the Regulatory Strategy and Planning domain is "Participates in SOP development and training related to them." Behavioral indicators for this competency include "Identifies the need for new regulatory procedures and SOPs and participates in development and implementation, helps train stakeholders on current and new regulatory requirements to ensure organization-wide compliance, and assists other departments in the development of SOPs to ensure regulatory compliance." Developers will emphasize that the behavioral indicators cannot possibly encompass all the variations that exist from setting to setting and individuals should exercise judgment in which ones apply (Graber and Rothwell, 2010).
- For some, though, the competency model's inherent emphasis on behaviors makes it too difficult to see its application to his or her work tasks, and it is here that entrustable professional activities (EPAs) offer a solution.

EPAs first became prevalent in competency-based medical education because educators worried that although competencies excelled at describing a high-performing doctor's attributes, they did not describe the tasks that doctor should be expected to do. An EPA defines a discrete, easily measured unit of work. Thus, while competencies define a person, EPAs define that person's work.

For regulatory professionals, developers took the competencies, established what work outcomes should come from each, then created lists of sector-specific EPAs that, when taken together, described most of the work connected with that competency. Developers then grouped EPAs into logical clusters to make it easier for someone using the structure to readily identify overarching areas for development.

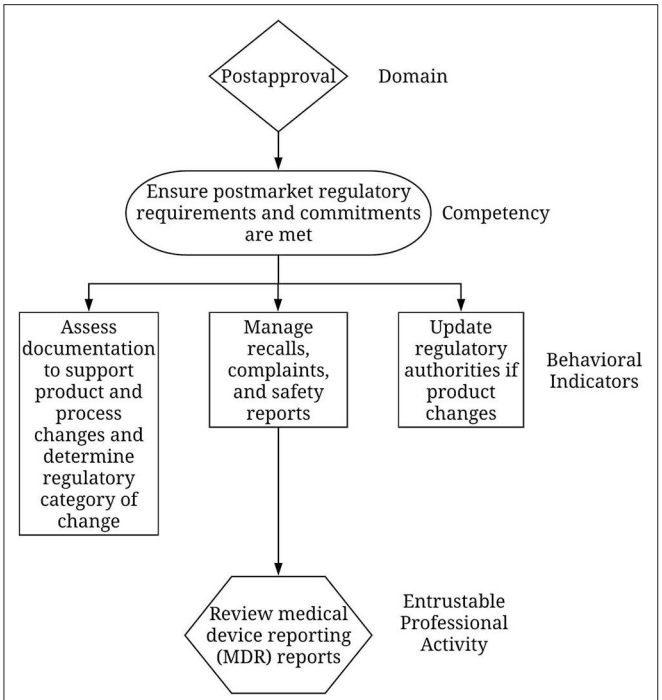

FIGURE 1 | Example of competency-behavioral indicator-EPA relationship.

Supplementary Material: 2018 Update to the RCF. **Figure 1** provides an example.

ADVANTAGES OF THE UPDATED RCF AND THE FUTURE OF COMPETENCY-BASED TRAINING FOR REGULATORY PROFESSIONALS

Developers expect the updated RCF will have a huge impact on the profession in multiple ways:

1) The multi-dimensional approach offers more flexibility and support, so those who are comfortable using competency models can use the RCF. Meanwhile, those who are new to the profession or may be the sole regulatory professional in his or her company will have the EPAs to highlight some of the tasks expected of regulatory professionals, as well as create clear metrics of ability related to career level.
2) The renewed emphasis on the RAPS Code of Ethics will underscore the vital role that regulatory professionals have in providing new, *safe* treatments for patients.
3) The additions of the professional, management, and leadership skills will create more well-rounded professionals who will be able to contribute more to their organizations' growth.
4) The more complete competency picture begins to create a better career "roadmap" for a profession that until this time has lacked a structural picture.
5) It also provides those who create training or other products to map their content against both behaviors and EPAs, which will help the individual achieve the level of mastery expected of the professional.
6) Related to the prior point, the updated model paves the way for a shift to competency-based training.

Traditional training development follows the ADDIE method, an acronym for Analysis, Design, Develop, Implement, and Evaluate. Analysis focuses on assessing needs, often for a large group of professionals, related to performing a specific task. Developers create content based on those needs with the assumption that all learners need the same information. The shift to competency-based education changes that process in some important ways.

Because competencies focus on high-performing individuals rather than what knowledge, skills, or tasks a specific role needs, analysis must shift to determining gaps that exist between a specific individual's performance level and the idealized competency. The result will be content tailored for the individual, rather than content that treats all workers as having the same level of need.

Because of this shift to understanding how the individual compares to the high performer, competency-based training will put more pressure on the individual to work proactively to identify gaps in his or her performance and seek training that addresses those gaps. It will also demand more communication between learner and supervisor, both to identify needs and to create mutually-acceptable ways to measure when or if the learner has filled those gaps.

The shift to competency-based training will be a slow process and will involve more work on the part of trainers, supervisors, and the individual regulatory professional. However, the connection to competencies will also result in a more well-rounded professional who will be fully conversant in the tasks in the regulatory lifecycle and in the communication, business, and leadership skills expected of all twenty first century healthcare professionals.

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WB performed the research and wrote the manuscript. All Supplementary Materials created by the Regulatory Affairs Professionals Society.

SUPPLEMENTARY MATERIAL

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Curriculum Transformation: From Didactic to Competency-Based Programs in Pharmaceutical Medicine

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As the complexity of the pharmaceutical industry increases and with the current disruptive forces affecting it, there is an increasing need for suitably-qualified personnel. Universities must respond to the need for graduates with the appropriate skills and knowledge to enable the transformation and future growth of this industry. Restructuring educational offerings to focus on graduate attributes, such as analytical and critical thinking, collaboration and problem solving, creativity, flexibility and self-direction in the context of the pharmaceutical industry facilitates the changes needed for future growth and viability. This paper discusses the process of program transformation to enable the development of graduates who can respond to these challenges in the pharmaceutical industry.

Keywords: pharmaceutical medicine, postgraduate education, curriculum development, online education, professional development, competency-based learning

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INTRODUCTION

It is said that we now live in a VUCA world: volatile, uncertain, complex and ambiguous; a scenario that can be applied across a number of industries including healthcare and education (Casey, 2014). Many of the disruptive forces affecting the healthcare industry today are also impacting education: digital disruption, the increase in flows of commerce, trade and people across national borders, and the rise of economic power in the East (Dobbs et al., 2015). The increasing voice of the patient and the rise of patient-centricity in drug development are mirrored by the increasing student voice and student focus in education. These factors are all leading to the emergence of new business models in the pharmaceutical and wider healthcare industries, and in education (McCluskey and Winter, 2012; Crow and Dabars, 2015; Downs and Velamuri, 2016; Godman et al., 2018). Both sectors need to become more agile and adaptable to meet the needs of their customers. In educating professionals entering or working in the pharmaceutical industry, we therefore need to design programs that can equip graduates to meet these challenges. To this end, the Master of Pharmaceutical Medicine program at UNSW Sydney has been transformed from a didactic, instructivist model to a fully online delivery model fostering collaboration and connections between students, enabling them to develop learning networks which will support them as they evolve in their careers. This paper will explore the transformation and renewal processes undertaken so far in transitioning this program to a professional -competency-based program that equips students with the skills, knowledge and connections needed to meet the rapidly changing needs of their chosen careers in pharmaceutical medicine, which is the medical science discipline concerned

with the discovery, pre-clinical and clinical development, evaluation, registration, safety monitoring, reimbursement and medical aspects of medicines used for therapeutic treatment (Daniels, 2011).

There is a growing need for qualified personnel to meet the demands of the pharmaceutical industry as therapeutics become more complex, the clinical and regulatory environments become more complicated, pricing environments become more restrictive and demands from patients and healthcare providers for education about therapeutics increase. With increasing pressures on the current operating model for large pharmaceutical companies and an increase in outsourcing critical functions, such as early stage research and development, clinical trials and regulatory affairs in Australia, there is an increased need for higher education institutions to deliver adequately trained employees who can hit the road running and provide immediate value to their employers (Ansell, 2013; Rasmussen and Foss, 2014). In 2017, the Australian federal government released the National Innovation and Science Agenda with the view to equip Australia for a transition from a low-value to a high-value manufacturing and services economy. One of the key pillars in this agenda is the need for skills and competencies development. In addition, the government has established a Medical Technology and Pharmaceuticals industry growth centre (MTPConnect) to drive the development of these industries. A central theme within the strategic agenda for this organization is skills development. The Commonwealth Scientific and Industrial Research Organization (CSIRO) has reviewed the future workforce growth required in this area. They have identified skills shortages in the sector and emphasized the need for greater training and education in areas such as clinical trials, advanced manufacturing, regulatory affairs and therapeutic product development (Commonwealth of Australia Department of the Prime Minister Cabinet, 2016; MTPConnect, 2016; CSIRO Futures, 2017). A more recent survey has identified a shortage in regulatory scientists in Australia (Cowles et al., 2017). Finally, the Medical Science Liaison Society has identified a 20% expected growth rate in the Medical Science Liaison role (a field-based medical affairs function) in the pharmaceutical industry over the next couple of years[1].

At the same time, higher education is undergoing a transformation in the way education is being delivered worldwide, with an emphasis on digital transformation and skills development to ensure graduates are equipped to meet the significant disruptive forces affecting many industries and societies today and into the future (Barber et al., 2013; Adams Becker et al., 2018). This transformation includes the significant growth in online education, which has been steadily growing over the past 14 years, driven recently by the Massive Open Online Course (MOOC) phenomenon (Kumar et al., 2017; Seaman et al., 2018). Part of this growth has been due to the transformation of old-style distance education programs into fully online programs, taking advantage of the affordances of the digital environment to foster collaborative, connected and immersive learning environment for students (Dabbagh and Kitsantas, 2012). Pedagogy has developed to focus on 21st-century skills development in digital and information literacy, collaboration and teamwork, analytical and problem-solving skills, flexibility and adaptability, creative and critical thinking, leadership, initiative and self-direction (Beetham and Sharpe, 2013).

With this context in mind, it was an opportune time to review the Master of Medical Science in Drug Development program, which had been provided by UNSW Sydney for 20 years. UNSW Sydney is one of Australia's largest research-intensive universities with a student body of over 50,000 and 6,000 staff. At the same time as this review of the program, the university was implementing an ambitious strategy that includes a commitment to academic excellence by embracing digital innovation, the formation of communities, inspired teaching methodologies, incorporating students as partners in educational reform, and closing the loop with greater feedback and dialogue between all partners in the educational endeavor.

The Drug Development program had originally been designed in an era focusing on didactic, instructivist education with an emphasis on knowledge delivery using early models of distance education that relied heavily on large volumes of paper-based notes, individual assignments and summative exam assessments (Anderson and Dron, 2011). To facilitate connections, students were required to attend the university campus four times per year for intensive weekend schools, which was a costly and inequitable activity, especially for students based around the country and overseas.

CURRICULUM TRANSFORMATION

To ensure the program remains relevant to the rapidly-changing pharmaceutical environment, a process was developed to systematically review and restructure the program based on sound pedagogical principles and the local pharmaceutical industry requirements (Chisholm, 2017). This process is shown in **Figure 1**. The process consisted of a thorough review of the existing program, benchmarking against similar programs, a stakeholder survey and review, a gap analysis, development of new courses, revision and rationalization of existing courses, formal approval by the university, and implementation followed by an evaluation of how the revised program is delivering against the plan. This process is cyclical and has the potential to be applied to any program of study needing updating.

The starting point for the development of the revised program was to articulate the mission of the program, which is to produce graduates with the knowledge and skills to make a meaningful contribution to medicines research, development and access, working across the pharmaceutical industry, academia and government, with the goal of improving the health and wellbeing of the community. Therefore, the program was aimed at people wanting to pursue a range of career possibilities in pharmaceutical drug discovery and development, medical device development, preclinical testing, clinical trials, drug safety and pharmacovigilance, regulatory affairs, medical and scientific communications, medical affairs,

[1] http://www.themsls.org/

product compliance or health technology assessment within industry, regulatory agencies, academia or government health departments. Students enter the program with a variety of prior qualifications and knowledge: healthcare professionals (physicians, pharmacists, nurses, veterinarians), scientists with undergraduate qualifications, other Masters' degrees or PhDs (in pharmacology, medicinal chemistry, pharmaceutical sciences, molecular biology, biochemistry, immunology, microbiology, medical science, biological science) and a small proportion with arts, psychology or law degrees.

Besides a thorough review of the existing content, a benchmark analysis of existing programs was conducted to identify areas of commonality and consensus. Stakeholders were surveyed to refine the elements needed for the revised program, identify gaps in coverage of the existing program and look at the future directions of the industry, the skills and knowledge that would be required by graduates in their careers (Allen and Chisholm, 2018). A gap analysis using all of this information helped to frame the program level learning outcomes (PLOs) for the revised program. Additionally, the PLOs were required to meet the Australian Qualifications Framework (Australian Qualifications Framework Council, 2013). The PLOs that were developed are listed in **Table 1**. They also reflect those outlined by the International Federation of Associations of Pharmaceutical Physicians (IFAPP) and Pharmatrain (Silva et al., 2013; Payton et al., 2013; Kerpel-Fronius et al., 2015; Dubois et al., 2016; Criscuolo, 2017[2]), but with the added competences of collaborative team work, development of digital and information literacy skills, an emphasis on development of a personal ethical framework, a global outlook and a thorough understanding of the pricing of new therapies. The emerging importance of the medical affairs role was recognized, and a new course was developed within the restructured program to address this gap in education (Moss et al., 2015). The revised program now consists of the following courses: introduction to the pharmaceutical industry, clinical trials, clinical trials management, Australian regulatory affairs, international regulatory affairs, pharmacovigilance, medical affairs, health technology assessment in Australia, advanced health technology assessment, pharmaceutics, general therapeutics, cancer therapeutics and an internship course. All courses and the program have been formally approved

[2]https://www.pharmatrain.eu/guidelines.php

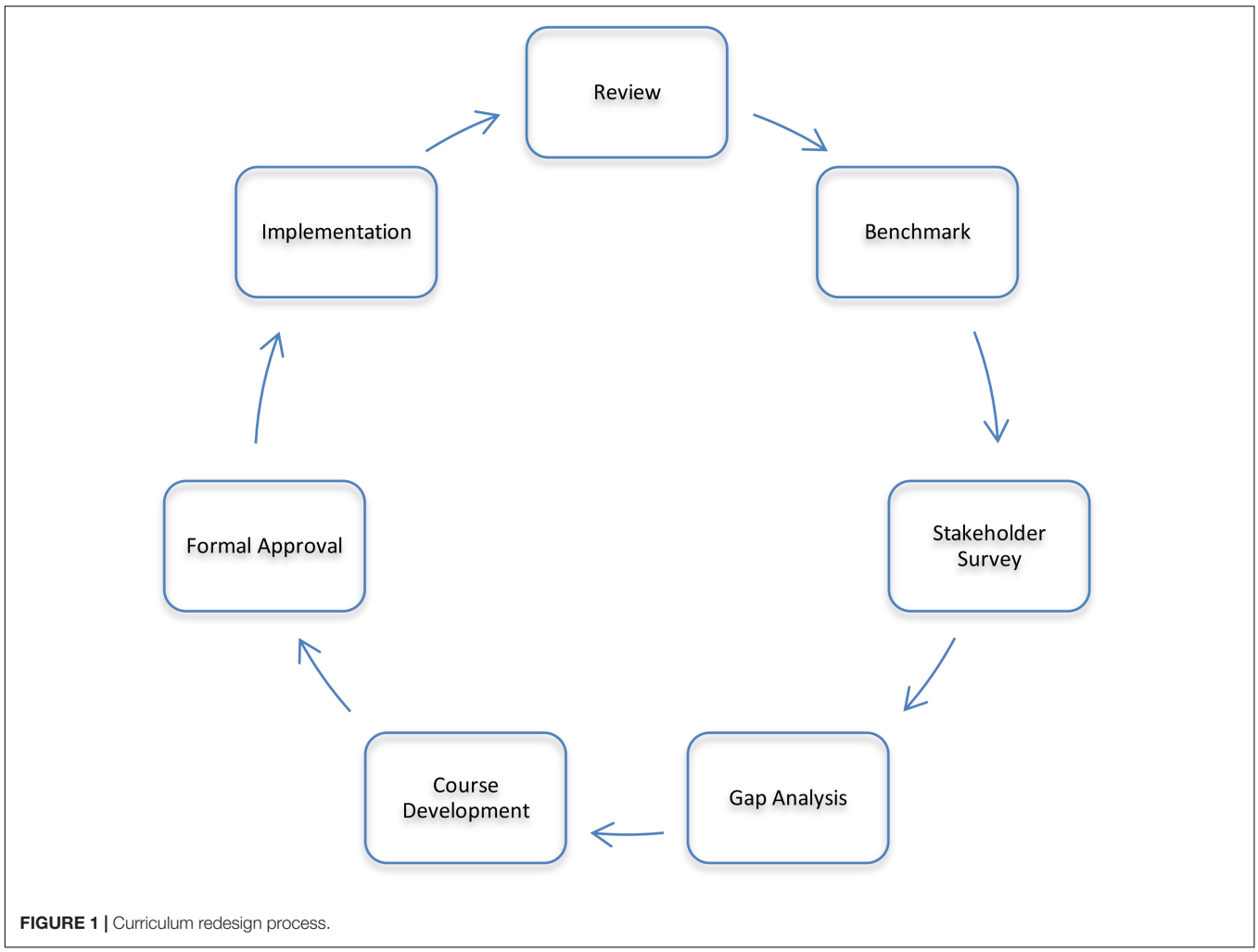

FIGURE 1 | Curriculum redesign process.

by the university and implemented since 2016. The revised program structure and course descriptions are available in the university handbook[3, 4]. Previous versions of the handbook are also accessible on the university website. Prior to this year, each course ran for one semester of approximately 14 weeks duration. From 2019, each course will run for a term of approximately 10 weeks duration, as the university has moved to a trimester academic calendar. The amount of content, activities and assessment tasks remain unchanged in this transition.

The redevelopment of courses within the program followed a competency-based model that included bringing together teams of academics, industry experts, alumni and current students, as described by Drago et al., 2016. Pedagogical theories on how new knowledge is integrated during the learning process and how collaborative learning enhances this formed the foundation for course design (Vygotsky, 1980; Gersick et al., 2000; Siemens, 2005; Lim and Honey, 2006; Rajagopal et al., 2012; Yuan and Kim, 2014). Therefore, the activities and assessments that students now undertake require them to utilize the new knowledge and skills they are developing to produce an assessible item (Koohang et al., 2009). After all, "It's not what we do but what students do that's the important thing" (Biggs and Tang, 2011). Another powerful method for encouraging students to integrate their new knowledge and skills is by reflective practice and all courses contain a reflective practice element (Schön, 1983; Boud and Molloy, 2013; Naraynassamy, 2015).

In their courses, students form communities of practice with the others in their course by contributing to the weekly discussion forums and working together in teams to complete assessment tasks and activities designed into the curriculum (Wenger et al., 2002). However, students also reach out beyond these groups to other students, alumni and teachers of their courses, as well as their professional networks, including their work colleagues. Students are encouraged to form these wider connections during their learning to enhance and cement the knowledge and skills they are developing in each course. All of these connections form part of the student's personal learning network and contribute to their continued learning beyond their graduation, becoming life-long learners (Moses and Duin, 2015; Wald, 2015).

The other important element in redesigning programs is to ensure there is constructive alignment between the program-level learning outcomes, the course-level learning outcomes, the activities and assessments that students undertake (Biggs and Tang, 2011; Fink, 2013). Courses are delivered online using the Moodle learning management system (Conde et al., 2014). The course design on Moodle follows the principles of the RASE system (resources, activities, support, evaluation) developed by Mirriahi et al. (2015). Authentic activities are designed into each course and include active learning and problem-based scenarios focussed on real life situations to develop problem-solving and critical thinking skills (Herrington et al., 2003). As an example, in a course on regulatory affairs, students are required to formulate an appropriate strategy for the registration of a new product, as one of the course-level learning outcomes that meets the program-level learning outcome of advanced disciplinary knowledge and practice. In order to meet this learning outcome, students have an assessment task where they are provided with a scenario and asked to prepare a report to their managing director outlining the regulatory strategy that they will pursue to obtain registration of the product described in the scenario. The scenario is a complex one where students need to integrate their understanding of two separate regulatory systems in Australia in order to determine the most efficient pathway forward. Aligning the activity, course and program outcomes like this ensures that the students meet them and graduate with the skills and experience required to undertake their roles in the pharmaceutical industry. As a

[3]https://www.handbook.unsw.edu.au/postgraduate/programs/2019/9370?q=9370&ct=all

[4]https://www.handbook.unsw.edu.au/Pharmacology/browse?sa=c2ce43204f0f5b00eeb3eb4f0310c77f

TABLE 1 | Program-level learning outcomes.

Advanced disciplinary knowledge and practice	Graduates will be able to demonstrate an advanced understanding of pharmaceutical medicine and the development process for new therapeutic products and apply their knowledge to new developments and approaches within this area.
Enquiry-based learning	Graduates will have the ability to ask the appropriate questions, find relevant information using their digital and information literacy skills and develop the required plans and documents to facilitate their contributions to the development and maintenance of therapeutic products.
Cognitive skills and critical thinking	Graduates will be able to understand, critically appraise and apply information and literature in the field of pharmaceutical medicine to inform development of new therapeutic products or strategies for success of new and existing products.
Communication, adaptive and interactional skills	Graduates will demonstrate the ability to effectively communicate complex, relevant subject matter relating to pharmaceutical medicine to diverse audiences. They will have the appropriate skills of flexibility and adaptability in working collaboratively with others in teams to achieve specified outcomes in a time-bound environment. Graduates will show leadership and initiative in areas of their focus within pharmaceutical medicine.
Global outlook	Graduates will have a thorough knowledge and understanding of the global arena in which therapeutic products are developed, regulated, priced and marketed.
Ethics	Graduates will reflect on and critique the role of ethics in the therapeutics industry and develop a personal ethical framework for working within the area of pharmaceutical medicine.

TABLE 2 | Assessment tasks for one course before and after restructure.

PHAR9101 (2013)	PHAR9101 (2019)
Quiz 10%	Group project – online wiki 40%
Individual responses to online exercises 10%	Individual essay assignment 30%
Individual assignment (3 parts) 40%	Online discussion forum contributions 15%
Invigilated final exam 40%	Individual reflective journal 15%

further example of the evolution of assessment tasks in the program, see **Table 2** below, which describes the assessment tasks for this course before and after the restructure. Detailed marking rubrics have been developed for each assessment task to ensure consistency of marking and to help students understand the requirements of the task. Assessment tasks are designed around real-life activities that students will conduct in their work such as writing reports, reviewing a dossier of information for a regulatory submission, or designing a clinical trial protocol.

The only synchronous activities scheduled are the webinars, which are held once a week, in the evenings, to facilitate student participation. Course moderators and tutors often present a lecture and discuss case studies with students during these sessions, and these conversations continue in asynchronous discussion forums which are moderated by the tutors. In several courses, students are required to give presentations in the webinars and lead discussion on their presentations. The internship course provides hands-on experience for students wanting to deepen their practice in a particular area, such as regulatory affairs, medical affairs, clinical research, etc. Placements are available to students in companies, with the regulator or academia. This aspect of the program enables students to develop level four competencies on Miller's pyramid by documenting performance integrated into practice (Miller, 1990).

The program is delivered fully online using the affordances of the Moodle learning management system and the internet (Harasim, 2000). Drivers for transition to an online delivery mode included:

- The ability to maintain currency of information in a fast-evolving industry
- A desire to improve collaboration between students located distantly from each other (an essential skill for working in the multinational pharmaceutical industry)
- A desire to increase self-evaluation and peer-evaluation (Boud and Molloy, 2013)
- The need to equip students with 21st century skills: digital and information literacy, critical and creative thinking, problem-solving, persistence, collaboration and teamwork, flexibility and adaptability, leadership, initiative and self-direction (McCluskey and Winter, 2012).

IMPACT OF THE PROGRAM TRANSFORMATION

The impact of changes to the program has been measured initially by both qualitative and quantitative methods. Success of the program transformation process has been and continues to be evaluated using student satisfaction feedback, analysis of their active engagement in the learning activities, assessment grades and employment outcomes. To date, there has been an increase in student engagement and collaboration throughout the program. This is seen with the increased numbers of posts to online discussion forums, which have increased from approximately three posts/student/course to 12 posts/student/course between 2015 and 2017. As well, students are responding to each other's posts and developing deep conversations around the course topics and scenarios provided in these discussion forums. Furthermore, students value the opportunity to engage and learn with each other: "*The Discussion Forums continue to offer great learning opportunities and the chance to bond with other students*". Students now undertake one group-based assessment task in each course throughout the program and this also fosters development of a sense of community, which is essential to the success of online learning programs (Gersick et al., 2000). These group-based tasks enable students to develop the networking and collaborative skills needed for a successful career in the pharmaceutical industry. The internship course will continue to be reviewed against Miller's pyramid to capture competency in action in the workplace.

Overall student satisfaction ratings across the program have increased from 4.3+/−1.2 to 5.1+/−0.4 (from a total score out of 6) between 2013 and 2017, providing evidence that students are seeing the benefit of the new alignment and learning and teaching style. Student grades have increased very slightly over the transition to a fully online program, showing consistency in learning even though student cohorts have changed over the years with slightly more now transitioning from another career. Academic staff teaching into the program have undertaken further postgraduate study in higher education. Industry- and government-based casual lecturers who currently teach on the program have significant experience with over 60% having appointments at director level or above in their own workplace. This greater expertise of all the teachers in the program is reflected by the higher student satisfaction ratings.

Finally, graduate employment levels are high for the program, with approximately 87% of graduates working in industry by their graduation (up from between 33 and 50% working in industry on entry to the program). In addition, approximately 80% of those who were working in industry at entry to the program managed to transition roles into the one they wanted or gained a promotion by graduation, including some who have taken promotions to positions based overseas. Further evaluation of the impact of the program transformation is planned and will include long-term follow-up of students after graduation, particularly reviewing transfer of learning to the workplace and career progression (Miller, 1990; Kirkpatrick and Kirkpatrick, 2006). This review may also result in further changes to the program as it evolves in-line with the evolution of the practice of pharmaceutical medicine.

CONCLUSION

In conclusion, the Master of Pharmaceutical Medicine program at UNSW Sydney is now delivered as a fully online program using the affordances of the digital environment to develop

capable graduates ready to take on challenging careers in the pharmaceutical industry. Their capabilities are developed through authentic learning experiences involving active experiential learning using problem-based scenarios focused on real-life situations to develop problem-solving and critical thinking skills. Additionally, students are learning in a connected environment that mirrors many of the interactions and situations they will face in their workplace, as we become more globally connected and work increasingly in digitally connected teams. As the working world changes, so too must the roles of educators and higher education continue to evolve. Thus, the delivery mode of the program is agile and able to be quickly adapted to meet future industry needs for skilled graduates, with Faculty acting not only as knowledge-experts, but as learning facilitators, for our students.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

OC was responsible for the concept and writing of this paper and takes full accountability for the content.

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Evolution of Ethical Principles in the Practice of Pharmaceutical Medicine From a UK Perspective

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Pharmaceutical medicine has evolved to be a distinct medical scientific discipline over time. Pharmaceutical medicine has distinctive features related to complex innovative medicines development activities in an often commercially focused competitive environment. This sometimes uneasy mix of professionalism and commercialisation demands of its medical and scientific researchers alike, a focus on strict adherence to ethical standards, guidelines, practices and behaviors in the interest of delivering new, effective, high-quality lifesaving and life-enhancing medicines quickly and reliably to patients in need. To support the speciality, codes of ethical standards and practices have been developed, with several being recently updated. These various codes are outlined in this paper along with relevant historical perspectives and interrelationship with concepts of professionalism. Reflecting the longer history of pharmaceutical medicine as a speciality in the UK and experience of the authors, there is a focus on the UK for the historical perspectives.

Keywords: pharmaceutical medicine, professionalism, ethical standards, biomedical research, ethical guidance

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BACKGROUND

The last five decades has witnessed an increased involvement of the medical profession in the development, introduction and maintenance of medicines. Alongside this has come a greater recognition of the multi-disciplinary nature of the development of medicines, as well as increased regulatory oversight of the processes and procedures involved. In relatively recent times, pharmaceutical medicine has evolved as a medical scientific discipline dedicated to the discovery, development, evaluation, registration, monitoring and the medical aspects of marketing of medicines (Stonier et al., 2007). In 1976 the Royal Colleges of Physicians of Edinburgh, Glasgow and London established the first Diploma in Pharmaceutical Medicine to be gained by examination after a 2-year training course for pharmaceutical physicians. Despite having physicians working for pharmaceutical companies, contract research organizations and regulatory agencies worldwide during this period, there has been limited awareness of the discipline by many academic and national medical associations, contributing to a slow recognition of pharmaceutical medicine as a distinct medical specialty. A pharmaceutical physician is a trained expert on the medical aspects of research, development, evaluation, registration, safety monitoring, and marketing of medicines in the best interests of patients.

Professional Organisations

There is vigorous debate about what characterizes a professional group or profession, but the following factors are generally regarded as the most important among various authors: a) the possession of abstract specialized knowledge; b) a high degree of individual autonomy; c) authority/influence over customer groups and subordinate occupational groups; d) a degree of altruism; e) a distinction from other occupational groups by higher status and higher pay (Greenwood, 1957; Hashimoto, 2006; Saks, 2012). Professions also are largely self-regulating in the approach they take to ensure that members acquire and maintain the skills and knowledge necessary to perform their role. It is recognized that individual professionals often lose a degree of autonomy when they are employed by large organizations or in government agencies; degrees of authority and influence are also likely to be diminished in such settings. These hindering factors for the professional can also come about from new government regulations and demands of third-party payers that restrict autonomy and influence. Such hindering factors may be more common for pharmaceutical physicians compared to patient-facing clinicians and perhaps argue for the greater need of these individuals to be supported by professional organizations.

The International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) was created in 1975 and currently has some 30 affiliated national professional membership associations, representing around 7,000 pharmaceutical physicians and other biomedical professionals involved in medicines development; with the incorporation of non-physician groups being a relatively recent development. IFAPP is a non-profit organisation with the mission to "advance Pharmaceutical Medicine by enhancing the knowledge, expertise and skills of pharmaceutical physicians and other professionals involved in all scientific disciplines involved in the discovery, development, processing and usage of medicines as well as experimental and clinical research worldwide, leading to the availability and appropriate use of medicines for the benefit of patients and society".

In the UK, the Faculty of Pharmaceutical Medicine (FPM) was founded in 1989 as a faculty of the three Royal Colleges of Physicians of the UK. It is a professional membership organisation and standard-setting body, with around 1,500 members and fellows, a quarter based outside the UK. There are currently some 150 pharmaceutical physicians undergoing post-graduate pharmaceutical medicine specialty training (PMST) through the FPM, and over 360 have achieved the outcome Certificate of Completion of Training (CCT) since pharmaceutical medicine was recognized as a medical specialty in 2002. This certificate allows them to be entered onto the specialist register of the UK General Medical Council.

ETHICAL CODES AND GUIDANCE

One characteristic of a profession, especially a healthcare-related profession, is that the behavior of its members is guided by a formal code of ethics. Pharmaceutical medicine is unusual in embracing two parallel but converging ethical frameworks: one concerning individual medical practice, and the other regarding the physician's role in clinical research.

Ethical codes concerning individual clinical practice have evolved since the time of Hippocrates. The principal purpose of such guidance is to assure the best interests of patients and members of the public. These interests must be protected above the need for income and advancement for healthcare practitioners themselves.

The development of clinical research ethics has followed a different path owing to its comparatively recent appearance. The ethics of clinical research have developed reactively, in response either to scandal or to novel scientific techniques (Faden and Beauchamp, 1986; Berg et al., 2001; Emanuel and Grady, 2007; Kimmelman, 2009). Thankfully, the modern trend is towards proactive modification of ethical codes. No longer are they merely to prevent a repeat of sins from the past but are instead forward-looking.

Such codes ideally support individual members of a profession to maintain high professional standards. To achieve this they share two common features:

- They must be prescriptive to a large degree. A descriptive or analytic moral framework provides insufficient support for an individual practitioner. Endorsing and proscribing certain behaviors gives clarity.
- They are based on mid-level ethical principles such as those proposed by Beauchamp and Childress (Holm, 1995; Beauchamp, 2003). Such principles allow for common ground when discussing ethical dilemmas with other stakeholders.

Medical practice ethics for clinicians and researchers come from three levels: global, national, and local. Global codes of ethics include those of the World Medical Association and CIOMS. Most national bodies also produce ethical guidelines for physicians engaging in patient care and in research with ethics codes for individual clinical practice now embedded in national medical regulatory bodies. In the UK the General Medical Council (a regulatory body) and the British Medical Association (a trade union) both provide guidelines on ethics. Many regulatory guidelines and practices (e.g. CIOMS) have worldwide applicability and irrespective of whether or not the concerned physicians have a specialist registration in pharmaceutical medicine.

Local institutional guidelines—often informal or even unstated—are equally important. While many research institutes have policies and procedures relating to ethical research, the tone of research in a hospital, pharmaceutical company, or research facility may be set by a community of peers or by a few senior researchers. Institutional pressure on individual decision-making is well recognized. "Breaking ranks" with established tradition can have unpleasant repercussions.

The shortcoming of the traditional approach is that most codes focus on the moral guidelines of a single profession. However, most pharmaceutical physicians now work in, and are highly reliant on, cross-functional, inter-disciplinary teams to

deliver their ultimate goals. The new Ethics Framework from IFAPP seeks to address this shortcoming and applies to scientists as well as physicians working in pharmaceutical clinical development and research arenas. IFAPP recommends that education in ethics should be integrated into the various training courses provided for individuals in these fields. Achievement of professional excellence can then be fostered, and self-identity and professional aspirations supported.

Why a Specific Code of Ethics for Pharmaceutical Physicians?

There are many codes of practice for healthcare professionals, differing by country, by culture, and by role. Berwick and others have called for a unified code of ethics for everybody involved in healthcare, but it seems that such a code may be too broad to help the individual practitioner (Berwick et al., 1997). Many ethical duties apply to all doctors, but we consider that there are two main reasons why a specific code of conduct for pharmaceutical physicians is warranted: their regular involvement in clinical trials of experimental medicines, and their work in commercially focused organizations.

Many clinicians engage in research at some point in their careers, but for only a few is it the mainstay of their job. Pharmaceutical physicians, however, are almost certain to have regular involvement with clinical trials. This can range from early phase trials with experimental medicines, through to late phase confirmatory and post-authorization studies. This heavy involvement in clinical trials is a distinguishing feature of pharmaceutical medicine.

Pharmaceutical physicians also have different communities from other clinicians. Clinician-researchers in hospitals or academia are swimming in the same ethical waters as their peers and co-workers. They are also likely to have been mentored by another clinician-researcher and to have implicitly bought in to a shared set of values. In contrast, pharmaceutical physicians often work independently from other clinicians, and are embedded within cross-functional teams.

Pharmaceutical physicians frequently have a business element to their job, or work for pharmaceutical companies that rely on commercial success. They can find their role involving conflicts between commercial imperatives and ethical decisions. Many pharmaceutical physicians also work outside of hospitals or academic centers where a code of medical ethics is part of the institutional culture. In these latter cases a physician's research work remains connected to their clinical practice, and both these elements of work are embedded within an institutional framework that is highly focused on the patient and on biomedical research. There is no over-arching need to make a profit and hence less need to focus on applied or use-inspired research.

For a pharmaceutical physician in a commercial organization a clash of values can take many forms, perhaps most clearly where for purely commercial reasons a company discontinues development of a drug that seems highly promising. A physician can indeed advocate for continued development, and here ethical and pro-social arguments compete directly with a broader financial interest. Physicians in industry tend to have little freedom to choose or direct the research in an organization. We note of course that the work of a physician in any setting is often constrained by environmental financial factors: for reasons of cost, some procedures or medications may not be available in a particular country, region, or hospital. However in these cases the ethical argument is around resource allocation, and any trade-off is against the well-being of other patients rather than the profit of a private company.

Pharmaceutical physicians working for government agencies can also face organizational pressures. Regulatory agencies have strong cultures, are often part of other governmental agencies, and there can be implicit or explicit pressure to approve or reject new medicines. The physician is acting on behalf of the state rather than on behalf of an individual patient. There are also close ties between the regulator and the industry itself. As the House of Commons Health Committee noted, "the relationship between the industry and the MHRA is naturally close. There are regular interchanges of staff, common policy objectives, agreed processes, shared perspectives and routine contact and consultation" (United Kingdom House of Commons Health Committee, 2005).

IFAPP International Ethics Framework

The new IFAPP International Ethics Framework for Pharmaceutical Physicians and Medicines Development Scientists was formerly known as the International Code of Ethical Conduct for Pharmaceutical Physicians, published in 2003. It was revised in 2016 considering the rapidly changing and increasingly complex scientific environment of medicines innovation and need to adapt ethical conduct to scientific progress. The present revision aims to provide an ethical framework for both pharmaceutical physicians and medicines development scientists about how to manage pro-actively difficult, and frequently new situations responsibly before they become major problems (Kerpel-Fronius et al., 2018). The new environment has led to re-organization of medicines development teams, with closer, more integrated involvement of specialized basic research groups. Advanced therapies including gene and cell therapies, or tissue engineering cannot be applied in clinical practice without fully integrating basic scientists into the development and treatment teams.

Pharmaceutical physicians have always collaborated with other members of research and development teams as well as with regulatory, marketing and other colleagues in the pharmaceutical industry or regulatory agencies. It is important to address the ethical responsibilities of the entire medicines development team including both basic research and clinical research experts.

We note that pharmaceutical companies are increasingly including ethical practice in their values and mission statements. There is a global shift towards increasing transparency and promotion of ethical practice within the pharmaceutical industry itself (Shaw and Whitney, 2016).

Pharmaceutical physicians and medicines development scientists must always remain aware that the interests of patients and their own employers are best served by an

objective scientific attitude and a rigorous ethical approach. IFAPP recognizes that this may place practicing pharmaceutical physicians and scientists in positions that demand considerable determination, and an ethical code can play a vital role in enabling them to reconcile their professional lives with their personal values.

The ethical framework recognizes that some ethical issues are only relevant to pharmaceutical physicians, and an increasing number of challenges must be faced jointly with scientists. For both groups it should be their primary objective to ensure the protection of the dignity, rights, needs and interests of the research participants.

The bioethical principles of Beauchamp and Childress—respect for autonomy, beneficence, non-maleficence and justice—provide a foundation for determining the ethical behavior of both physicians and scientists working in medicines research. They form a basis for balanced ethical judgment in conflict situations, although it is evident that experts in medicines development weigh these principles differently according to the circumstances. Additional ethical principles of relevance to research and development activities include vulnerability, subsidiarity and solidarity, as well as consideration of the duties to the society regarding objective-setting and appropriate research conduct.

The IFAPP Ethics Framework intends to provide an educational background to guide both pharmaceutical physicians and medicines development scientists through their day-to-day deliberations and decision-making whether they practice within a company, contract research organization, academic department, regulatory authority, or work on ethics committees or as independent consultants.

CIOMS Ethical Guidelines for Biomedical Research

The fourth version of the CIOMS Ethical Guidelines for Biomedical Research was published in 2016 (CIOMS). The scope of the 2002 Guidelines was broadened from "biomedical research" to "health-related research" and the guidelines are now entitled 'International Ethical Guidelines for Health-related Research Involving Humans'. Despite some debate about the way the guidelines were developed, they are broad and inclusive (Schuklenk, 2017; Schuklenk, 2017).

As also noted by IFAPP several developments had taken place since the last version of their Ethical Guidelines, among them:

- The Declaration of Helsinki had been updated to the 7th revision (2013).
- A heightened emphasis on the importance of translational research.
- A need to clarify what counts as fair research in low and middle-income country settings.
- A greater emphasis on community engagement in research.
- An awareness that exclusion of potentially vulnerable groups in many cases has resulted in weaknesses in the evidence base.
- The increase in the research use of big data.

Following extensive evidence retrieval and synthesis processes, international consultation and peer review the latest CIOMS guidelines form a comprehensive reference tool. The document is over 100 pages and includes 25 guidelines with commentary plus appendices providing guidance on items to be included in a protocol and essential information to be provided to prospective research participants.

FPM Guiding Principles and Good Pharmaceutical Medical Practice

The FPM Guiding principles were developed in 2010 and updated in 2014 to provide an ethical framework for medical practitioners practicing in the field of pharmaceutical medicine, whether in industry, regulatory bodies or an academic environment (Bragman et al., 2010). These were derived from the original publication and full report published in 2006 (Bickerstaffe et al., 2006; Bickerstaffe et al., 2006). The document clarified that pharmaceutical physicians are bound by the same ethical standards that apply to all doctors. However, their work leads to some very specific ethical considerations that may not be fully explored in ethical codes based on clinical practice. It clearly placed the doctor's duties to the wider public and the protection of patients and research participants ahead of responsibilities to an individual employer. It also emphasizes the importance of medical leadership in promoting ethical principles and accountability in decision-making.

In 2013, the UK General Medical Council published the Good Medical Practice (GMP) document (General Medical Council, 2013). This forms the core guidance for all registered doctors in the UK and centers on four Domains. 1: Knowledge, skills and performance; 2: Safety and quality; 3: Communication, partnership and teamwork; 4: Maintaining trust. It is supported by a range of explanatory guidance covering fundamental ethical principles that most doctors will use every day e.g. Consent and Confidentiality. There is guidance that may be more relevant to doctors working in certain specialties, or about specific situations that not all doctors will encounter in their career.

The focus of the GMC guidelines is on clinical specialties; pharmaceutical medicine, as highlighted earlier, does bring very specific ethical considerations which may not be fully explored in ethical codes based in clinical medicine. Hence the FPM established a working group to evaluate the needs of pharmaceutical physicians, and later built on the GMC document to create Good Pharmaceutical Medicine Practice (GPMP) in 2008 and updated November 2014, tailored towards the pharmaceutical physician, and explaining how requirements in GMP should be interpreted for those working in pharmaceutical medicine (Good Pharmaceutical Medical Practice, 2014).

GPMP is being reviewed again with an updated document expected in 2020. The Faculty will need to decide if the older Guiding principles document is now redundant as a separate document and should be withdrawn. This is not straightforward as the Guiding Principles were designed foremost to guide

those working in pharmaceutical medicine, while GPMP arises from broader medical codes. The underlying principles that guide the protection of patients and research participants, namely; Individuals Come First, Professional integrity and Confidentiality, are completely in line with GMP requirements, however the Guiding Principles goes further in some specific areas. Examples include the need for training in medical ethics and international good clinical practices (GCPs) and promotion of these principles by leadership and example, as well as seeking to raise standards of ethical conduct amongst colleagues and fellow staff. Regulatory Work and Marketing Work are drawn out with examples, e.g. ensuring proposed labeling of a medicinal product accurately reflects the clinical trial data, there is openness and transparency in publication and sharing of research results, and awareness of possible business and commercial pressures. Other specific points are for promotion of all medicines to be supervised by pharmaceutical physicians and be based on objective, ongoing assessment of all the available information. Promotion must be in accord with the labeling and not involve the use of undue pressures or inducements of any nature on healthcare workers to prescribe a product.

Although a document based on GPMP has more impact and authority for UK registered doctors, the Guiding Principles have the great merits of being relatively short, developed specifically for Pharmaceutical Medicine, and relevant globally wherever FPM fellows and members work.

Embedding Ethical Attitudes in Pharmaceutical Physicians: Clear Communication, Training and Support

A significant challenge is how to embed codes of ethics and standards into the way that professionals think and behave on a day-to-day basis.

Clarity is an important feature of ethical codes. The content must be communicated to those who require it, and length and ease of reading of documents can be substantial barriers to their reading and understanding.

The FPM has made ethical practice a part of its curriculum. All those who train in pharmaceutical medicine must, over the course of their PMST programme, demonstrate integrity and ethical practice. This begins the process of new pharmaceutical physicians developing an ethical grounding.

The FPM sought to develop the original guiding principles as a short document, refer to them in Faculty and other meetings, send printed copies to members and send periodic links to electronic copies available on the website. Alongside the Code and supporting Continuing Professional Development, the FPM has launched a support network and commitment to support those working in the pharmaceutical medicine arena to make the best decisions relating to ethics, probity and integrity.

Future Considerations

We expect ethical principles related to pharmaceutical medicine and health research in general to continue to evolve with time. With the future advancements in treatment approaches and paradigms this seems inevitable and particular ethical issues will surround areas such as advanced therapies utilizing cell and gene therapies and regenerative medicines as these receive an ever increasing number of approvals. Therapies based on gene editing techniques will also bring their own ethical issues which as a specialty, we will have to face. The use of 'Big Data', AI and Real World Data will also require special considerations as far as ethics is concerned; questions such as who actually owns and who should own these data, and how consent is obtained to use such data will need to be debated.

In conclusion, the last fifty years has seen great strides in the development of codes of ethical standards and practices plus support structures for the speciality of pharmaceutical medicine and medicines development. It seems clear that ethical issues and principles will continue to be ever present and continue to evolve. Newer entrants into pharmaceutical medicine should also be encouraged to participate in this evolution. We support the sharing of the principles of medical ethics at undergraduate level for future physicians and healthcare scientists.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Specialist in Medicines Development (SMD) as a Vocational Program in Pharmaceutical Medicine: The Japanese and Italian Experience

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The growing complexity of the drug development process requires globally recognized professionals who have not only completed the cognitive path of competence, i.e. the specialized post graduate course in Pharmaceutical Medicine, but suggests that these individuals should join a vocational training program in order to consolidate the seven competencies which characterize a competent Pharmaceutical Professional. The Specialist in Medicines Development (SMD) program developed by the IMI project PharmaTrain and further supported by the IMI project IMI-TRAIN can be considered a prototype vocational program. In order to test the SMD value, it was implemented in two countries, Japan and Italy. The preliminary results, after three years of its implementation, are here summarized, and some initial recommendations are offered to all other countries which may consider to establish this program.

Keywords: vocational training program, pharmaceutical medicine, PharmaTrain, specialist in medicines development, IFAPP, SIMeF

INTRODUCTION

Professionals with medical and non-medical backgrounds work in the complex environment of medicines development in different functions and are trained on-the-job, leading to an array of competencies across multiple domains (Silva et al., 2013). Some of them may have attended one of the university-based post-graduate diploma or master courses in Pharmaceutical Medicine, offered since many years in several European countries, and in Japan, South Africa and few other countries. However, there is a growing consensus that a diploma or master title in Pharmaceutical Medicine is just a starting point: professionals involved in the drug development process should know in depth its entire process, and also be able to apply their knowledge reliably and creatively in their daily working environment in order to drive innovative R&D efficiently. Such vocational training is defined as a "training that emphasizes skills and knowledge required for a particular job function" (https://www.skillsportal.co.za/content/what-exactly-vocational-training).

In the UK, Switzerland and Ireland a vocational program for physicians has been implemented, leading to a national medical board certification in Pharmaceutical Medicine. But no globally

recognized educational path nor structured qualification process is available for physicians in other countries, and for not medically qualified professionals working in medicines development (Imamura et al., 2019). Indeed, it was recently published (Redfearn, 2018) that "certified principal investigators (CPIs) and clinical research coordinators (CRCs) do better work compared with their peers who hold no certification": however this certification should be extended to all professionals involved in the drug development process, and should be harmonized.

One of the first projects established by the European Public-Private Partnership Innovative Medicines Initiative (www.imi.europa.eu) was the "PharmaTrain" project (2009–2014, Grant Agreement number 115013) (PharmaTrain, 2019). Its first objective was the syllabus harmonization and the quality improvement of postgraduate education in Pharmaceutical Medicine/Medicines Development Sciences, resulting in a PharmaTrain recognition system for diploma and master courses. The second objective was the development of a competency-based, workplace-centered education and training certification program in Medicines Development, comprising a knowledge base covering the PharmaTrain Syllabus for Medicines Development Science, delivered and assessed through modular curricula, and the acquisition and demonstration of competencies for medicines development across seven domains of the competency curriculum (Silva et al., 2013). Participants in this mentored, vocational program should acquire knowledge and competencies within a framework of assessment, appraisal and annual review of progress and achievements. On completion, participants will receive the SMD Certificate from the global PharmaTrain Certification Board (gPCB).

A pilot implementation of the SMD concept was funded by IMI from 2014 to 2016 as part of the IMI-EMTRAIN ENSO project "IMI-TRAIN" (Grant Agreement number 115015) (IMI-TRAIN, 2019). This project integrated the results and organizations of all training-related IMI projects with the aim to create an IMI Education and Training Infrastructure with a common IT portal to a joint platform for Continuous Professional Development (CPD) tools including new online training modules, and the SMD certification program as a role model for other specialist title certification programs like in safety sciences or pharmacovigilance and epidemiology. In a dedicated Work Package, the infrastructure for the SMD program was developed in cooperation between academic teaching institutions and pharmaceutical companies to enable national implementation by a local Pharmaceutical Medicine organization. Ideal candidates for the SMD program were either professionals with a significant experience (more than 4 years of professional activity in drug development) or professionals who, after obtaining the title of master/diploma in Pharmaceutical Medicine, were in the position to start their professional career in drug development.

The country selected for the SMD pilot implementation was Italy, due to its well established post-graduate education infrastructure in Pharmaceutical Medicine, a relevant pharmaceutical industry, the interest of the Italian Association of Pharmaceutical Medicine (SIMeF) to create such career development opportunities for their members, and the availability of two master courses (Catholic University of Rome and Bicocca University in Milan) which received the recognition of PharmaTrain Centres of Excellence (Criscuolo, 2010).

One of PharmaTrain's consortium partners was IFAPP, the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine, and another course recognized as a PharmaTrain Centre of Excellence was the master course in Pharmaceutical Medicine at the University of Osaka. The Japanese Association of Pharmaceutical Medicine (JAPhMed) expressed interest in joining the pilot initiative with their own resources.

Experiences made with implementation of the SMD concept in Italy and Japan are here illustrated and commented.

The SMD Pilot Program in Japan

In accordance with global PharmaTrain SOPs, a national PharmaTrain Certification Board (nPCB) was established with representatives from JAPhMed, ACRP (Association of Clinical Research Professionals Japan), and EFPIA (European Federation of Pharmaceutical Industry Association Japan), in 2016. Upon initiation of the second year (2017), professors and directors from national universities and national medical centers joined the nPCB, which currently consists of eight members. The nPCB is established and acknowledged by the gPCB to meet the requirements of the local SMD program, according to legal or regulatory requirements, geography and culture. All nPCB members are qualified directors or have a master level, or above, in a life science or medical field, are actively working in or consulting in the area of medicines development science or pharmaceutical medicine, are experienced in at least two speciality domains of the SMD curriculum over a period of not less than 10 years, and are actively undertaking Continuing Professional Development (CPD) in their own area of competence.

Under the nPCB, a SEG (SMD Executive Group) was established by the nPCB, to undertake the executive actions of the nPCB to implement, monitor and administrate the SMD program. At present, eight members of the SEG regularly meet and discuss progress of the program and any issue to be discussed at the nPCB meetings, which are held on quarterly basis. In order to align with global directions and to standardize the methods of assessment, a series of SOPs were developed. Forms to report learning activities and their assessment results were also developed for standardized reporting. Since the development of the nPCB and the SEG, the program has been promoted on the JAPhMed website, showing program entry criteria, methods for regular review and assessment of competency by the mentor in the workplace, and the final certification to be granted by the gPCB.

To introduce this new program, ten participants were invited for a free submission, six of them from the industry and the other four from academia. Four new trainees and mentors are registered in the second year as fee-paying participants. The SMD program entry criteria require participants to have completed a formal education (BSc, MSc, MD, PharmD, RN, DV, PhD, or equivalent) in a discipline in life science or healthcare e.g. medical doctors, pharmacists, biologists, chemists, biometricians, certified nurses, as well as to hold a job related to research, development or medical

marketing of medicinal products. At present, one trainee was assessed as competent by her mentor and her records were examined by the SEG with a third party review by experts. Having reviewed her assessment records, the nPCB recommended to the gPCB to assign the SMD title. After review by gPCB, this trainee was certified as the first SMD since the development of this international program.

The program asks trainees to complete theoretical training (specialty knowledge base) in medicines development in an accredited course covering the entire PharmaTrain Syllabus (The PharmaTrain Federation), with assessments and certified outcome, as well as the evidence over 4-year period of gaining practical training and competencies in medicines development. This has been the main difficulty for the SMD program in Japan, because there was no systematic education in medicines development until 2013 when the first PharmaTrain educational course was developed in collaboration with the Osaka University. Although there are many relevant courses and lectures in this area, most of them lack assessments and do not fully cover the PharmaTrain Syllabus. Therefore, after the baseline assessment of competency, the trainee and the mentor had to develop a plan to fill the gap in education. The second difficulty that most trainees have experienced are the career changes of mentors and/or themselves. Once it happens, trainees must find alternative mentors who can succeed to supervise their program, but it is not always easy to identify dedicated mentors in their workplaces. Although the Japanese job market is less fluid as compared to other countries, increasing numbers of corporate mergers and acquisitions, as well as organizational changes are the constant risk for the SMD program.

The SMD Pilot Program in Italy

In Italy, Regulatory Authorities have addressed, at least in part, the need for structured post-graduate education in Pharmaceutical Medicine for professionals working in this environment. In fact, according to an Italian law dated 2008 (Italian Ministry of Health, 2008), all professionals working in a CRO must follow a dedicated training program, which can be considered as completed by the achievement of a University master title in Pharmaceutical Medicine. This law was instrumental for the implementation of several master courses in Pharmaceutical Medicine in several Universities all over the country (Criscuolo, 2017). Currently, the number of professionals in Pharmaceutical Medicine with a master title is approaching 1500. These professionals are the ideal candidates for the SMD program: in fact, the gPCB decided that Italian professionals holding a master title, which means that they achieved a significant background knowledge in drug research and development over a period of 1.5 years and performed a work-place based stage of at least 6 months, need only to be followed up in a mentored fashion during 2 years of their initial professional activity to achieve the SMD title.

The initial process of the SMD program in Italy was very similar to the steps established by our Japanese colleagues: the main difference is in the nPCB composition. In fact, in order to get more visibility and an independent body, SIMeF opened this Board to several organizations with whom there is a long lasting collaboration. SIMeF identified, among its executives, four senior members for the nPCB, who had the task to support all planned activities. But the nPCB was also composed by the following additional members: one delegate from AIFA (the Italian Drug Agency), one delegate from each of the two Universities where there is a master in Pharmaceutical Medicine which got the PharmaTrain recognition of Centre of Excellence (Rome Catholic University and Milano Bicocca University), one representative of SIF (the Italian Association of Pharmacologists), one representative of FADOI (the Italian Association of Internal Medicine) and one representative of a patients association. In total, the Italian nPCB is therefore composed of ten members, and the majority of this Board is made of independent professionals.

The first meeting of the nPCB was held in the premises of AIFA, the Italian Drug Agency, in order to give more value to the event, and to underline the independent role of this body: further meetings were and are held every six months, and are mainly arranged *via* teleconference. Great efforts were put in place to disseminate the information about the SMD program, and to attract registrations: a very low fee was also enforced (first year free, second and further years at 500 euro), having in mind that most applicants were supposed to pay this fee by themselves. All relevant information about the SMD opportunity was posted on the SIMeF website on a dedicated page; in addition, at every SIMeF seminar, an SMD leaflet was distributed to all participants; finally, in every issue of the SIMeF bimonthly newsletter, an advertisement about the SMD opportunity is published.

Notwithstanding these significant efforts, and also considering the large number of potential applicants holding a master title, two years after the implementation of the SMD program in Italy, we have only four professionals who registered. Three of them are from the same pharmaceutical company, working in the Medical Affairs dept, and their registrations were strongly stimulated by their Medical Director, who greatly appreciated the program's aims and contents. The fourth applicant is a professional holding the master title, who joined the program in order to get a more pragmatic training in Pharmaceutical Medicine.

DISCUSSION

The preparation of the SMD concept started in PharmaTrain in 2013 but was only completed in the IMITRAIN project in 2016, therefore the two pilot experiences of the SMD implementation, in Italy and in Japan, started only 3 years ago. Therefore, it may be too early to draw some conclusions. However, some initial comments may be appropriate, having also in mind that additional National Associations of Pharmaceutical Medicine may be interested to support this program in their countries.

Indeed, the basic idea of the vocational SMD program is very appealing: professionals educated theoretically in Pharmaceutical Medicine may gain great competence from the SMD program, because they receive the unique opportunity, while on their job, to gain experience in practice about the full process of drug development, to become familiar with the consequences of decisions made during this path and to have to interact with professionals of several areas, in order to complete their

TABLE 1 | Statement of competences in pharmaceutical medicine. IFAPP/PharmaTrain 2012 [from Silva et al. (2013)].

Domain I: Discovery medicine and early development. To identify unmet therapeutic needs, evaluate the evidence for a new candidate for clinical development and design a Clinical Development Plan for a Target Product Profile.
Domain II: Clinical development and clinical trials. To design, execute and evaluate exploratory and confirmatory clinical trials and prepare manuscripts or reports for publication and regulatory submissions.
Domain III: Medicines regulation. To interpret effectively the regulatory requirements for the clinical development of a new drug through the product life-cycle to ensure its appropriate therapeutic use and proper risk management.
Domain IV: Drug safety surveillance. To evaluate the choice, application and analysis of post-authorization surveillance methods to meet the requirements of national/international agencies for proper information and risk minimization to patients and clinical trial subjects.
Domain V: Ethics and subject protection. To combine the principles of clinical research and business ethics for the conduct of clinical trials and commercial operations within the organization.
Domain VI: Healthcare marketplace. To appraise the pharmaceutical business activities in the healthcare environment to ensure that they remain appropriate, ethical and legal to keep the welfare of patients and subjects at the forefront of decision-making in the promotion of medicines and design of clinical trials.
Domain VII: Communications and management. To interpret the principles and practices of people management and leadership, using effective communication techniques and interpersonal skills to influence key stakeholders and achieve the scientific and business objectives.

understanding in the seven domains required for being a competent pharmaceutical professional (Silva et al., 2013; Dubois et al., 2016; Criscuolo, 2017; Imamura et al., 2019) (see **Table 1**).

The recognition of the benefits of a candidate's SMD certification to an employer takes time; and also the relevance for attracting high potential professionals by offering the SMD mentoring program in their organization still needs to be fully appreciated. Therefore, National Associations of Pharmaceutical Medicine, universities and industry associations which are promoting this initiative must continue to stimulate professionals, especially the younger ones who have obtained a master title in Pharmaceutical Medicine, to join the SMD program, and to make employers aware of the relevance of these professionals for their organization's success. In the long run this will clearly demonstrate the significant importance of having competent professionals devoted to drug development, in a worldwide environment.

Finally, the SMD program is an important additional step to achieve the PharmaTrain vision of modern competence which says "Better trained postgraduate professionals working in medicines development and regulation worldwide produce better medicines".

AUTHOR CONTRIBUTIONS

DC conceived the manuscript, and wrote *Introduction*, the section about Italy implementation, and conclusions. KI contributed to the idea of the manuscript, and wrote the section about Japan. IK contributed to the idea of the manuscript, and wrote the section about PharmaTrain and IMI roles in SMD preparation.

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Evolution of the Development of Core Competencies in Pharmaceutical Medicine and Their Potential Use in Education and Training

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The evolution of postgraduate vocational education and training in pharmaceutical medicine is described alongside the growth of this scientific-medical discipline and profession for the development of new medicines. Over the past 50 years, whilst the training of competent professionals for their work has been paramount, this has paralleled the need to engage with the rapid and complex changes in R&D technologies, patient and healthcare system needs, and the ethical and regulatory obligations applied to the development of medicines throughout their lifecycle. The move from unstructured training to formal programs with syllabus, curricula and assessments for certification, has been accompanied by educational changes to outcomes-based, learner-centered, competency-based programs. The evolution of education and training along with the development of the set of 57 core competencies for professional practitioners in pharmaceutical medicine are described within the competence framework of seven domains: discovery of medicines and early development; clinical development and clinical trials; medicines regulation; drug safety and surveillance; ethics and subject protection; healthcare marketplace; communication and management. The application of the core competencies in a harmonized, international platform of education and training in medicines development at the undergraduate, postgraduate and continuing professional development levels would invigorate the potential for having a competent workforce with the intent to provide faster access to better and appropriate medicines for patients worldwide.

Keywords: pharmaceutical medicine, syllabus, curriculum, core competencies, PharmaTrain, IFAPP, Faculty of pharmaceutical medicine

BACKGROUND

Pharmaceutical medicine is the medical scientific discipline concerned with the discovery, development, evaluation, registration, monitoring and medical aspects of marketing of medicines for the benefit of patients and the public health (Faculty of Pharmaceutical Medicine, 2019).

The employment of doctors in medical departments and R&D operations of pharmaceutical companies, the need for clinicians and prescribers to be involved in the development of marketed medicines, the increased influence of payers and providers, the proven needs of involving patients in their treatment, and the need to consider clinical and cost effectiveness in making medicines available to patients and the public, have all served to increase the engagement of the biomedical profession in the development, introduction and maintenance of medicines (Cromie, 1993; Gabbay, 2003; Young and Stonier, 2011). Over the last 50 years pharmaceutical medicine evolved from these needs for medical engagement in the development and commercialization of medicines to become a broad scientific-medical discipline. In some countries and territories pharmaceutical medicine remains as an adjunct discipline, in some others it has become a formal, legal medical specialty as part of the medical profession. Pharmaceutical medicine is thus a global and multi-disciplinary field, involving in its work a wide range of biomedical graduates, scientific and technical groups together along with support from administrative, legal and financial professions. The term 'medicines development science' is used alongside 'pharmaceutical medicine' to acknowledge this multi- professional discipline.

The academic system has been historically slow in recognizing the needs for formal postgraduate education in medicines development and thus the first initiatives were left to the professional bodies.

A group of pioneer pharmaceutical physicians in the United Kingdom came together to form the Association of Medical Advisers in the Pharmaceutical Industry in 1957 (AMAPI, later British Association of Pharmaceutical Physicians, BrAPP) as a vehicle for mutual support and, for a long period, to promote non-structured education and training for its members.

Pharmaceutical medicine was organized as a novel discipline through the creation of the International Federation of Associations of Pharmaceutical Physicians (IFAPP) in 1975 followed by the introduction of the first structured training program organized by University of Wales Institute for Science and Technology (UWIST; now Cardiff University), under guidance from a joint committee of AMAPI and the Association of the British Pharmaceutical Industry (ABPI). This program evolved and in 1978 became the *Postgraduate Course in Pharmaceutical Medicine* (Luscombe and Salek, 2001).

These initiatives paralleled the creation of the *Diploma in Pharmaceutical Medicine (DPM)* an examination- based certification established in 1976 by the Royal Colleges of Physicians of the United Kingdom aiming to advance the discipline and to establish standards (Binns, 1976; Smith, 2000). These developments were the start of the organized profession of pharmaceutical medicine.

This was followed by many countries with professional associations encouraging the creation of vocational postgraduate education and training. The incorporation of 30 national associations was coordinated through IFAPP, mostly concerned with the recognition of pharmaceutical medicine as a medical specialty at the national level and fostering initiatives for postgraduate education and continuing professional development (CPD). As a result, a limited number of postgraduate programs are offered in a few countries in Western and Central-Eastern Europe, Latin America and Asia with relative success.

The early training programs and courses in pharmaceutical medicine followed a Syllabus of topics across the discipline. The Syllabus in Pharmaceutical Medicine was derived from an understanding of the knowledge concerning the clinical testing and licensing of new medicines and their introduction into medical practice and was developed for the *Postgraduate Course in Pharmaceutical Medicine*. The knowledge-based Syllabus, essentially a list of topics defining the universe of knowledge in and boundaries of pharmaceutical medicine, was developed initially in the United Kingdom and had frequent revisions as a result of the evolving discipline, to incorporate newer topics and to re-emphasize others (Shelley, 1991; Stonier and Gabbay, 1992). With the PharmaTrain project (see below) the opportunity was taken to develop the Syllabus as a global, aligned syllabus for these knowledge-based initiatives. The current version is the PharmaTrain Syllabus in Pharmaceutical Medicine/Medicines Development Science (V2.0 January 2018) and is recommended as a platform for global education and training (Faculty of Pharmaceutical Medicine, 2019).

TOWARD THE DEVELOPMENT OF CERTIFICATION THROUGH A COMPETENCY-BASED TRAINING CURRICULUM

Recognizing the growing acceptance of the discipline among medical professionals, BrAPP proposed that the UK Royal College of Physicians establish a Faculty of Pharmaceutical Medicine. The Faculty was inaugurated in 1989 as a new professional group and standard-setting body representing the medical discipline of pharmaceutical medicine in the United Kingdom (Goldberg and Smith, 1985). The foundation of the Faculty established the need for entry criteria for new members and reconciled training needs for entry via its certification program, the *Diploma in Pharmaceutical Medicine-DPM*, granted by the Royal Colleges of Physicians of the United Kingdom.

There was however a concern that the academic knowledge base itself was not a total reflection of the professional attributes required to practice safely within the scope of a newly proposed medical specialty, and that specific personal skills and business management knowledge should be recognized and incorporated into training programs (Stevens, 1987).

In 1992 a survey was conducted amongst the 810 combined membership of the Faculty and BrAPP. The survey aimed to identify items of knowledge and skills considered important in the daily work of pharmaceutical physicians, to identify training needs and timing, and to explore the relationship between training needs and actual training received. An outcome of this survey led to opportunities to develop

new training programs, as a few items of knowledge and skills were identified which were considered important to practitioners but for which there was a shortfall in training. Such items fell across the specialty medical and technical areas of medicines' development, but the majority were related to personal transferable skills and to business management (Stonier and Gabbay, 1992). The outcomes of this survey also served as a foundation to define the professional competencies.

The Faculty and Joint Committee on Higher Medical Training (JCHMT) of the Royal Colleges of Physicians worked together to pursue the medical specialty recognition for pharmaceutical medicine and the introduction of a specialist training program. As a result, Pharmaceutical Medicine Higher Medical Training (HMT) was designed around six practical domains with continuous assessment. HMT would be an accredited vocational program in order to meet local opportunities for direct in-workplace experience and training, and for indirect training through interactive external courses.

The proposed HMT program comprised two parts, basic HMT and advanced HMT, with the individualized program completed in an indicative 4-year period. Basic HMT included the knowledge and applied knowledge (cognitive competency) described in the Syllabus for Pharmaceutical Medicine. This was assessed through the examination for the DPM, which remained the assessment of the knowledge- based component for HMT and for the subsequently titled Pharmaceutical Medicine Specialty Training program (PMST).

Advanced HMT was a workplace-based experiential program covering six domains of practice within pharmaceutical medicine: regulation of medicines, early and late clinical development, data management and statistics, drug safety and surveillance. A further domain of interpersonal, management and leadership matters was recognized and added to address general transferable skills applicable to practice in pharmaceutical medicine.

The Faculty produced draft outlines for the six practice-based specialty modules and in 1998 commissioned the University of Keele to undertake a Delphi exercise to determine their content (Millson et al., 2000).

There was a total of 364 statements of knowledge and skills at the start of the Delphi process, and these were gathered to form the six curricular domains with a level of achievement given for each constituent competency. The outcomes of each Delphi exercise on the six modules were analyzed at the University of Keele and published (Commentary, 1999; Millson et al., 1999; Phelan et al., 1999; Boardman et al., 2000).

With the results of the Delphi exercise for the competencies in each of the six specialty domains the Faculty's Specialist Training Committee developed and added knowledge, skills and attitudes/behaviors statements to the competencies to form the curricular content of six practical modules in advanced training in pharmaceutical medicine (Faculty of Pharmaceutical Medicine, 1999; Faculty of Pharmaceutical Medicine, 2000).

This competency-based curriculum was a relatively recent innovation and had benefited from new outcomes-based educational techniques. Commentators at the time noted that few medical specialties had been so original in determining the curriculum for the training of their specialists (Editorial, 2000).

In parallel with the development of the competency-based workplace-centered HMT program, steps were taken through the Faculty and JCHMT to obtain formal, legal listing of pharmaceutical medicine as a medical specialty in Schedule 2 of The European Specialist Medical Qualifications Order 1995, restricted to the United Kingdom. This was achieved on April 17, 2002.

The advances in education and training in the United Kingdom were closely followed by IFAPP. The IFAPP Council for Education in Pharmaceutical Medicine (CEPM) was established in 2002 to promote education in pharmaceutical medicine in collaboration with its member associations, to advise new and established members on setting up courses and examinations, to harmonize established courses for diplomas in pharmaceutical medicine, and to foster the recognition of pharmaceutical medicine as a medical scientific discipline.

FURTHER DEVELOPMENT OF THE CURRICULUM IN UNITED KINGDOM; PHARMACEUTICAL MEDICINE SPECIALTY TRAINING (PMST)

In 2005, the medical regulator's intent was to replace HMT with a new updated curriculum developed with all medical specialties. The new curriculum was renamed *Pharmaceutical Medicine Specialty Training* (PMST) as a vocational program aimed to achieve competence in the workplace.

The PMST curriculum covering knowledge, assessed through the Diploma in Pharmaceutical Medicine examination, practical competencies and generic aspects was designed for training of pharmaceutical physicians who enter the specialty of pharmaceutical medicine after four years of post-qualification clinical training and experience.

PMST is available for doctors working in pharmaceutical companies, clinical research organizations, academic clinical research units or regulatory bodies to gain a *Certificate of Completion of Training* (CCT) from the medical regulator, the General Medical Council.

In addition to some updated competencies, reflecting experience in practice, and clarification of terminology of knowledge, skills and attitudes/behaviors the new PMST included workplace-based assessments, and an e-portfolio to record evidence, assessments, achievement and progress in the training program. PMST is thus a competency-based program delivered through the workplace, known as the Local Educational Provider (LEP), together with an Educational Supervisor (mentor) allocated to each trainee.

In 2019 there are 360 specialist pharmaceutical physicians who have completed PMST and have a place on the GMC's specialist register in pharmaceutical medicine. There are 140

physicians enrolled currently in PMST working in over 60 LEPs approved for training.

Whilst the PMST program might satisfy the present requirements of the curriculum for specialist training in the United Kingdom, vocational education and training is a dynamic process, subject to change as a result of evolving working practices and new skills with professional requirements which might transform both the curricular domains and their constituent competencies.

DEVELOPMENT OF CORE COMPETENCIES IN PHARMACEUTICAL MEDICINE. THE ROLE OF IFAPP AND PHARMATRAIN

The development of a competency-based curriculum in the discipline of pharmaceutical medicine depended firstly on agreeing the broad domains relevant to the field and within them defining and building the competencies with the knowledge, skills and attitudes/behaviors which meet the objective of the competency and are also mapped to the knowledge-based Syllabus for Pharmaceutical Medicine.

With the advent of competency-based education there was a realization within IFAPP of the need to develop and maintain a list of core competencies to meet the requirements of the profession, and a responsibility to orientate and focus the discipline and related academic programs for the development of competent professionals and influence the profession of pharmaceutical medicine (Stonier et al., 2007).

Twenty eight IFAPP member associations when surveyed showed that only 20% of their membership had received postgraduate education in pharmaceutical medicine (Silva et al., 2012, 2013). Similarly, surveys conducted in the United States among pharmaceutical physicians revealed that the respondents lacked formal training in critical areas of drug development (Stonier et al., 2011).

One response to this lack of education and training was a call from the largest public-private partnership in biomedicine, the Innovative Medicines Initiative (IMI), to integrate existing expertise and further raise the quality of postgraduate education and training in pharmaceutical medicine for all professionals working in medicines development. In 2009 the 'PharmaTrain' project was awarded to a consortium of all European academic providers of pharmaceutical medicine courses, IFAPP, and experts from not-for-profit organizations and other universities offering training in this discipline. They collaborated with experts from the participating pharmaceutical companies on development of the PharmaTrain Syllabus (V1.0. 2010), in turn adapted from the Faculty, as well as harmonized curricula for a modular diploma base course, a master's degree and a CPD platform, aiming to align the opportunities for education and training in Europe. Nine quality criteria for course providers were defined and a course recognition system developed and implemented. The harmonized quality training program for post-graduate education in Medicines Development is now applied by PharmaTrain-recognized academic and training organizations in Europe and worldwide (Klech et al., 2012; PharmaTrain Manual, 2012).

Based on these activities, there is now firmer collaboration between all parties involved. A working group to start accruing core competencies was established within IFAPP's CEPM including representatives from PharmaTrain, academic institutions and IFAPP's member associations, with special interest and experience on quality improvement through education. A review and analysis of the core competencies published by academic groups or professional associations relating to pharmaceutical medicine was undertaken. A combination of bibliographic search and consultation with related groups was agreed, using a modified six- sigma approach to process improvement. The domains were identified through benchmarking, alignment and harmonization of domains and competencies from similar or related groups. The competencies developed by the Faculty formed the foundation for this exercise (Faculty of Pharmaceutical Medicine, 2010).

The critical issues considered were the areas and domains for competence, and their intrinsic and extrinsic validity; the descriptors for each competency and their relevance; the level of granularity and comparability with other disciplines and professions, and the level of anticipated expertise. The group focused on the cognitive aspects for each proposed competency and conducted a mapping exercise with the learning outcomes and curriculum for the PharmaTrain Diploma base course. The competencies were verbalized using the highest wording associated with the competence category in the revised Bloom's Taxonomy (Bloom, 1956). The final version of the core competencies was authorized at IFAPP's General Assembly in Barcelona, Spain November 17, 2012.

Resulting from this, seven domains of competencies were identified within the competence framework: discovery of medicines and early development; clinical development and clinical trials; medicines regulation; drug safety and surveillance; ethics and subject protection; healthcare marketplace; communication and management.

A total of 57 core competencies for pharmaceutical physicians and drug development scientists was included. The learning outcomes of the PharmaTrain Diploma base course were aligned (93%) with the competencies.

A Statement of Competence summarizing the competency domains was prepared (**Figure 1**). This is a concise description for a competent professional who can contribute to any stage of product life-cycle management (Silva et al., 2013).

From January 2015 to March 2016 the renamed IFAPP-PharmaTrain competency working group (IPCWG) revised the core competencies in a process like that conducted previously. The skills and behaviors associated with the applied knowledge for each of the core competencies were identified. IFAPP member associations engaged in a consultation exercise with the draft version, before a final set of full core competencies was agreed and adopted at the IFAPP House of Delegates Meeting in São Paulo in April 2016 (see **Supplementary Annex 1**).

The Pharmaceutical Physician / Medicines Development Scientist is able to:

- **identify unmet therapeutic needs, evaluate the evidence for a new candidate for clinical development and design a Clinical Development Plan for a Target Product Profile.**
- **design, execute and evaluate exploratory and confirmatory clinical trials and prepare manuscripts or reports for publication and regulatory submissions.**
- **interpret effectively the regulatory requirements for the clinical development of a new drug through the product lifecycle to ensure its appropriate therapeutic use and proper risk management.**
- **evaluate the choice, application and analysis of post-authorisation surveillance methods to meet the requirements of national/international agencies for proper information and risk minimisation to patients and clinical trial participants.**
- **combine the principles of clinical research and business ethics for the conduct of clinical trials and commercial operations within the organisation.**
- **appraise the pharmaceutical business activities in the healthcare environment to ensure that they remain appropriate, ethical and legal to keep the welfare of patients and research participants at the forefront of decision making in the promotion of medicines and design of clinical trials.**
- **interpret the principles and practices of people management and leadership, using effective communication techniques and interpersonal skills to influence key stakeholders and achieve the scientific and business objectives.**

FIGURE 1 | Statement of competence in pharmaceutical medicine/medicines development science.

The core competencies were revised and updated by the IPCWG in 2018, and as a result a few changes in skills and behaviors were included.

INTENDED USE OF THE CORE COMPETENCIES IN PHARMACEUTICAL MEDICINE

The core competencies can serve as a resource and guide for improving the accountability and quality of education and training in pharmaceutical medicine.

They were developed recognizing the distinctiveness and diversity in the complex world of medicines' development. The model may foster further detailed development and identification of sub-competencies that might be applicable to specific functions in clinical research and drug development.

The primary vision for this competency model is the availability of professionals who are more fully prepared to meet the challenges and opportunities in pharmaceutical medicine/medicines development science in the next decade.

Competency-based profiles of key jobs in medicines development can be prepared, and standardized job descriptions for different functions could be developed globally.

The effective implementation of training programs using the core competencies anywhere in the world may renovate drug development to be an efficient process integrated with product lifecycle management and resulting in the availability of better medicines. Several competency-based programs are currently in the planning phase (Chisholm, 2019; Schnetzler et al., 2019).

A knowledge-based online program *'Medical Affairs in Medicines Development'* sponsored by IFAPP and King's College London is now available to students worldwide. Its learning outcomes are aligned with the core competencies[1].

Developments of competency models are iterative processes, and the model described here will have to be updated regularly as the competencies are employed for professional, academic or self-assessment purposes. Continued dialogue regarding the use of the competencies, their relevance, and ongoing changes in the fields of pharmaceutical medicine and related drug development sciences will make the changes imperative. Competency sets generally have a lifespan of 3–5 years (Batalden et al., 2002; Calhoun et al., 2008).

Professional groups elsewhere in clinical research are working to define the roles and competencies of individuals working

[1] www.ifappacademy.org

in specific areas, including physician investigators, nurses, investigational site staff as well as other professions involved in regulatory affairs, project management, translational science and comparative effectiveness (Koren et al., 2011; Jones et al., 2012; Sonstein et al., 2014; The Global Health Network, 2016; Calvin-Naylor et al., 2017; ACRP, 2019).

The set of core competencies, together with the PharmaTrain Syllabus, serve as a guide to the IFAPP member associations and related institutions worldwide to develop undergraduate, postgraduate and CPD programs in pharmaceutical medicine/medicines development science.

AUTHOR CONTRIBUTIONS

All authors contributed both to the development of the ideas as well as to the writing of the manuscript and the linked **Supplementary Material**.

SUPPLEMENTARY MATERIAL

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Linking the Declarations of Helsinki and of Taipei: Critical Challenges of Future-Oriented Research Ethics

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Expansion of data-driven research in the 21st century has posed challenges in the evolution of the international agreed framework of research ethics. The World Medical Association (WMA)'s Declaration of Helsinki (DoH) has provided ethical principles for medical research involving humans since 1964, with the last update in 2013. To complement the DoH, WMA issued the Declaration of Taipei (DoT) in 2016 to provide additional principles for health databases and biobanks. However, the ethical principles for secondary use of data or material obtained in research remain unclear. With such a perspective, the Working Group on Ethics (WGE) of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) suggests a closer scientific linkage in the DoH to the DoT focusing specifically on areas that will facilitate data-driven research, and to further strengthen the protection of research participants.

Keywords: research ethics, data science, medicines development, privacy protection, data sharing, Declaration of Helsinki, Declaration of Taipei

1 INTRODUCTION

Expanding interests in data-driven clinical science in the 21st century have posed some critical challenges in the recent evolution of research ethics. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has endorsed renovation (ICH GCP Renovation, 2017) to facilitate utilization of reliable real-world data (RWD) for regulatory decision. This expands the usability of data derived from ordinary medical practice and research, as well as from health databases and biobanks. The World Medical Association (WMA) has since clarified some principles for these types of research but we believe it requires further clarity.

The WMA had established its paramount deontology of physicians to prioritize health and interests of a patient, as described in the Declaration of Geneva (WMA Declaration of Geneva, 1948) and the International Code of Medical Ethics (WMA ICoME, 1949), both issued in its second and third years

of foundation. Since the first adopted version of the Declaration of Helsinki (DoH) in 1964 until the latest update in 2013 (WMA Declaration of Helsinki, 1964), the WMA has refined its core principle to prioritize rights and interests of the research subjects, ahead of scientific research goals. To implement this principle, with multiple DoH amendments, the WMA established an international agreed framework of ethics committee approval of research protocols, and the requirement of informed consent from research participants. It was its 5th amendment in 2000 that the scope of the DoH was expanded. Rather than limited to research involving individual humans, it would also cover research on identifiable human material or data. Since then, its scope has also been extended to include a framework of publication ethics: conflict of interest disclosure, publication of both positive and negative research results, and study registration in public databases.

Furthermore, reflecting decades of discussions concerning biobank developments in several countries, the 2008 amendment of the DoH added paragraph 25. It required researchers to justify the waiving of informed consent for research using identifiable human material or data, which may be obtained from biobanks or similar repositories, conditional upon ethics committee approval. In 2016 the WMA adopted the Declaration of Taipei, on Ethical Considerations regarding Health Databases and Biobanks (WMA Declaration of Taipei, 2016) (DoT), revised from its first version in 2002, to complement the DoH. It would now cover "the collection, storage and use of identifiable data and biological material beyond the individual care of patients".

The scope of each of the two declarations is defined in both documents. However, it is not clear in the DoH how secondary or subsequent multiple use (we would describe these as "secondary use" hereafter) of data or material derived from "primary research" activity should be managed. From this point of view, we explored a way to clarify in the DoH to link with the DoT, as a part of our activities to promote ethical conduct of research (https://ifapp.org/working-groups/ethics-and-professionalism). The strengthened linkage to the DoT in the DoH, which is well-known worldwide as established principles for research involving humans, is required specifically for facilitating data-driven research while protection of research participants is maintained.

2 CROSSROADS OF DOH AND DOT

The DoT states that it provides "additional ethical principles" to the DoH. However, the DoH does not refer to the DoT. Therefore, it is a prerequisite to reference the DoT in any revisions of the DoH. Since the DoH deals with "research" and the DoT deals with "data/material collection", the frameworks of these two types of activities have been separately considered. Therefore, investigators who are engaged in research without explicit intention of biobank/database development may not be aware of the governance framework defined in the DoT. Meanwhile, there is an increasing number of cases where the sponsors/investigators of the research or third party outside of the specific research later come to be interested in secondary use of data/material derived from it. For this reason, where there is a possibility of future secondary use of data/material collected in a research project, this research should be conducted adhering not only to the DoH but also to the DoT.

The essential requirements of the DoT which should be recognized by the research community are: 1) Items of information for obtaining "valid" consent when data/material are collected in a Health Database (HDB) or Biobank (BB) are defined including, e.g., the purpose of the HDB/BB; returning results including incidental findings; 2) Robust governance process of HDB and BB are defined including, e.g., documentation; traceability; arrangement of ownership change or closure; privacy protection and discrimination prevention; Material Transfer Agreement (MTA), all of which should be informed to the candidate donor of the data or material (WMA DoT, 2016; Dhai, 2016; WMA What we do).

3 RESEARCH IN THE SCOPE OF THE DOT AND VALID CONSENT

Table 1 shows examples of HDBs and BBs and related examples of research and development (R&D) activities. Obviously, activities of development of HDBs, BBs and patient registries must adhere to the DoT.

Real World Data are being generated in the process of daily patient care, outside the scope of the DoH or DoT. However, recently, there has been an increasing number of activities for the development of HDBs to prepare anonymized or coded datasets for future secondary use. These activities are sometimes performed by commercial organizations under contract with a hospital/care organization, according to recently developed legal frameworks in various countries. The physicians' ethical obligations to adhere to the DoT must be implemented in such processing of patient data.

Research involving human participants has not been typically regarded as HDBs or BBs. However, sometimes a researcher may only envision a possibility of future sharing of individual data/material with other researchers after the primary research has been completed but has not considered to inform the ethics committee nor the candidate participant. Such consideration should indeed be described in the study protocol and informed consent form (ICF), clarifying governance framework in accordance with the DoT, to be assessed by an ethics committee. Once the planned future sharing of data/material with the relevant governance framework is approved by an ethics committee, a candidate participant can then decide whether to accept or refuse this secondary use. This consent should be separately obtained from the consent to participate in the proposed primary research. The candidate's decision whether to allow secondary use of data/material should not impact on possible participation in the primary research. Such consent does not mean traditional "broad consent" meaning "blanket consent" (Wendler, 2013) but "valid" consent as defined in the DoT.

Another aspect which needs clarification in the DoH is about the management of incidental findings (IFs). IFs are those identified during the research that are not primary objectives of the research project. Policy of reporting IFs is necessary part of valid consent in the DoT but it is not mentioned in the DoH. The right of an individual of taking option of knowing/not knowing the IFs should be assured in both DoH and DoT frameworks.

TABLE 1 | Examples of health databases and biobanks and examples of their utilization.

Types of health databases and biobanks with brief explanations	Related examples of expected R&D activities
1. HDBs and BBs: Project-based large-scale research resource development	Drug development lead candidate search
2. Patient registry: HDB development activity is sometimes associated with BB, focusing on one specific disease or intervention. Similar to cohort studies, but objectives are focused on research resource development rather than on simple prospective epidemiological research.	Rare disease drug development including lead candidate search. Alternative to control group of a clinical trial
3. Real World Data (RWD): RWD means data derived from ordinary medical practice. Recently, increasing number of repositories of de-identified data derived from RWD have been created.	New Drug Application (NDA) for new indication. Post-Marketing Surveillance (PMS) after expedited approval. Artificial Intelligence (AI) development
4. Research involving human participants: "Research" is not regarded as HDB or BB but there are increasing demands for secondary use from data/material obtained in the research.	Individual Participant Data (IPD) meta-analysis. Subgroup analysis of clinical trial results

TABLE 2 | Benefits and risks of IPD sharing.

Benefits/merits	Risks/demerits
"Maximize the knowledge gained from the efforts and sacrifices of clinical trial participants" (ICMJE)	Privacy risk of participants unless data to be shared would be "de-identified" participant data
"Strengthening the science that is the foundation of safe and effective clinical care and public health practice" (CIOMS)	Risk to researcher/sponsor of impact of re-analysis on their original finding or commercial interests
Possibility of independent re-analysis of clinical trial results, including systematic review as well as subgroup analysis for personalized medicine	Risk to public health - impact of unfair/invalid secondary analysis
Increase the transparency and credibility of clinical trials	Burden of researchers to prepare their data/material obtained in their research in format possible to be shared with others

Summarized from the statements of the organizations cited in this manuscript.

4 INDIVIDUAL PARTICIPANT DATA (IPD) SHARING AND TRIAL REGISTRATION REQUIREMENT

On the premise of the above-mentioned governance framework both by the DoH and the DoT, we should consider the importance of "individual participant data (IPD) sharing" along with registration of a data sharing plan to a publicly available database, exploring the policies and statements issued from several international organizations, as shown in the **Supplementary Material**. Moreover, it is crucial that future IPD sharing is planned at the beginning of a research project, should be disclosed to, and approved by, the concerned ethics committee and then the volunteered participants.

"Data sharing plan" means the policy and planning of the way how the researcher can share IPD obtained in the research with other researchers for secondary analysis. The International Committee of Medical Journal Editors (ICMJE) stated in 2017 (Taichman et al., 2017) that responsible sharing of de-identified IPD of interventional clinical trials would be an "ethical obligation" and requires clinical trials enrolling participants on or after January 1, 2019 to include a data sharing plan in the trial registration. ICMJE allows researchers to register such a plan as "not available (we do not share our data)", but each member journal editor may consider each plan during their editorial decision. Benefits and risks of data sharing are summarized in **Table 2**. Considering this situation, responsible IPD sharing should be recommended as an "ethical obligation" in the DoH.

There is another point to discuss concerning study registration requirement. A requirement of clinical trial outline information registration in a public database was stated by the ICMJE in 2004 (De Angelis et al., 2004) as a precondition for acceptance of a manuscript for publication of clinical trial results. This requirement was included in the DoH in 2008, and in the 2013 revision, the scope of the studies with a registration requirement was expanded from "clinical trial" to "every research study involving human subjects". However, earlier in this century, not only trial outline registration at initiation, but also result registration at completion in a public database, has become a regulatory requirement in the United States (US) (FDA Act, 2007; NIH DHHS Final Rule, 2016), the European Union (EU) (EU Regulation 2014), Japan (Clinical Trial Act, 2017; MHLW, 2017) and other countries. A substantial lack of compliance with these regulations has been reported (Goldacre et al., 2018; The Lancet Oncology, 2019; DeVito et al., 2020; Piller, 2020). The paragraph 36 of the DoH requires result publication, but this paragraph does not refer explicitly to result uploading in public database, thus, this paragraph is generally understood as a journal publication requirement. Given that journal peer review takes time, thus study results often fail to be disclosed in timely manner. Additionally, not all journals provide open access and therefore restrict information transparency. On the other hand, result registration in public registries could be enforced by regulatory

authorities, and be accessible in a timely manner to general public. The public disclosure practices compliance should be underlined as an "ethical obligation" in the DoH. The DoH should explicitly define it as a knowledge-sharing obligation concordance to the Declaration of Geneva (WMA Declaration of Geneva, 1948).

For the reasons as stated above, the DoH should include two additional requirements of study registration in a public database of 1) the data sharing plan at the initiation of and 2) full disclosure of results at the completion of a clinical trial.

5 DOT AS AN ETHICAL BASIS OF THE EUROPEAN UNION'S GENERAL DATA PROTECTION REGULATION (GDPR)

Besides the well-recognized benefits of IPD sharing, one of the most heavily discussed risks of individual data sharing is privacy risk. Especially after the implementation of the EU's General Data Protection Regulation (GDPR) (GDPR, 2016), the legal basis of secondary use of clinical trial data have been just under discussion between the European Commission (European Commission, 2019) and the European Data Protection Board (EDPB) (EDPB, 2018; EDPB, 2019). This regulation specific to the EU has great impact to the world because sharing personal data of the individual from the EU with countries outside the EU is governed by this regulation. Anonymized (de-identified) data is out of the scope of GDPR. ICMJE's statement on IPD sharing is about this type of data, and anonymization methodology has been standardized by some clinical trial-related initiatives (PhUSE, 2015) or by each academic society. However, genuine anonymized data may have more limitations, and processing personal data into anonymized ones before secondary use also requires a legal framework. Justification of secondary use of personal data, pseudo-anonymized and/or coded, is a prerequisite.

In terms of GDPR, there are two possible avenues for justification: a) application of its article 89 of the GDPR for scientific research allows waiver of explicit consent of an individual, subject to appropriate privacy protection; b) justifiable consent to secondary use in line with Recital 33 (GDPR Recital 33) of the GDPR, which can be interpreted as broad consent, being subject to "recognized ethical standards".

To provide justification to above mentioned both approaches, the WGE argues the combined use of DoH and DoT should be the ethical basis in the framework of GDPR for secondary use of IPD based in the following reasons:

(1) The EDPB already recognized the DoH as the ethical foundation of informed consent (EDPB, 2018), thus the DoT should be the foundation of valid consent for future secondary use of personal data;
(2) The EU Clinial Trial Regulation already defined such consent for secondary use separate from consent to clinical trial participation (EU Clinical Trial Regulation, 2014); and
(3) The Council for International Organizations of Medical Sciences (CIOMS) have already recognized "Broad informed consent" to secondary use in its guidelines (CIOMS, 2016).

6 CONCLUSION

Based on the above described analysis, the WGE proposes revisions of the DoH necessary to facilitate expanding data-driven clinical science while assuring continued protection of research participants as follows:

(1) The relationship between the DoH and DoT should be clearly described in the DoH. It should be clarified that not only intentional development of health-databases or biobanks, but any research activity must adhere to the DoT, where there is any possibility of secondary use or sharing with others of the data/material collected in the research.
(2) Any future plan of sharing of data and/or material obtained in the research should be clearly described in a study protocol and ICF to be assessed by an ethics committee and to enable the candidate participants to make decision whether to accept this secondary use. This consent should be separately and independently obtained from the consent to participate in the proposed research, without impact on possible participation in the primary research.
(3) The right of an individual to decide whether he/she wants to be informed of IFs should be assured.
(4) In addition to the study registration requirement, registration requirements of "data sharing plan" and "study results" in publicly available databases should be explicitly defined as critical elements of physicians' obligation of knowledge sharing.

The WGE believes this revision of the DoH to clarify linkage to the DoT will provide a solution for critical challenges of future-oriented research ethics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors contributed both to the development of the ideas as well as to the writing of the manuscript and the linked **Supplementary Material**.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Corrigendum: Linking the Declarations of Helsinki and of Taipei: Critical Challenges of Future-Oriented Research Ethics

Chieko Kurihara[1], Varvara Baroutsou[2], Sander Becker[3], Johan Brun[4], Brigitte Franke-Bray[5], Roberto Carlesi[6], Anthony Chan[7], Luis Francisco Collia[8], Peter Kleist[9], Luís Filipe Laranjeira[10], Kotone Matsuyama[11], Shehla Naseem[12], Johanna Schenk[13], Honorio Silva[14] and Sandor Kerpel-Fronius[15]*
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A corrigendum on

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In the original article, there were errors.

In the **abstract**, "(Declaration of Taipei)" was deleted; in the **1 Introduction** section, "1948, in its second year" was changed to "in its second and third years"; in the **4 Individual Participant Data (IPD) Sharing and Trial Registration Requirement section**, parenthesis before and after "Supplementary Material".

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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